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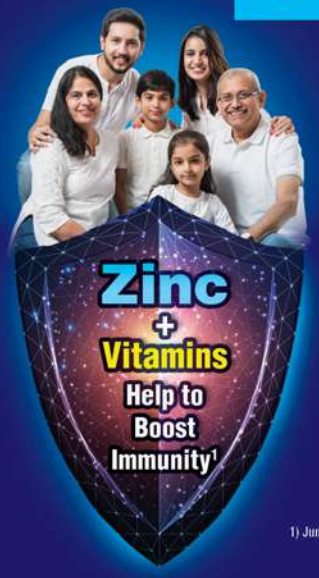

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Indian Pediatrics

November 2023 Volume 60 Number 11

CONTENTS

Indian Pediatrics, the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with monthly circulation of print/e-copies to over 34,000 pediatrician members. The journal is indexed in Current Contents/Clinical Medicine, Science Citation Index Expanded, Medline, PubMed, Indian Science Abstracts, getCITED, POPLINE, CANCERLIT, TOXLINE, Psych Line, and Dermline. The journal gives priority to reports of outstanding clinical and experimental work, as well as important contributions related to common and topical problems related to children and adolescents. Information for Authors is available on the website of the journal. *Indian Pediatrics* is available free online at *www.indianpediatrics.net*. There are no charges for publishing in the journal.

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Are We Doing Enough for the Girl Child?

UPENDRA KINJAWADEKAR
President, Indian Academy of Pediatrics, 2023
upen228@gmail.com

India accounted for 45.8 million of the world's 142.6 million "missing girls" over the past 50 years, referring to the females missing from the demography due to sex-selective abortions or infanticide. Further, India has the highest rate of excess female deaths, 13.5 per 1,000 female births, suggesting that an estimated one in nine deaths of females below the age of 5 may be attributed to postnatal sex selection. Along with China, India is the leading contributor to the global phenomenon of 'missing girls.' The fact that a deep-rooted preference for the male child has persisted in our society well within the twenty-first century is a matter of collective shame for all of us.

But why this preference? By all accounts, girls very often outperform boys in school academics, and we have brilliant examples of women leading nations, industries, business, science and innovation, literature and the arts. Yet we have a host of social and cultural constraints and norms that still hold us to this regressive mindset of considering women as inferior, second class citizens, and thus denying them equal opportunity. As I reflect on my own childhood, I can think of a number of ways in which my sisters were socialized far differently than I was. I never learnt to cook, for instance, relying on the women in my life to fulfil this basic life skill. In other such subtle ways, gender norms and roles are defined and perpetrated, and girls and women are held back from achieving their true potential. While some manifestations of this patriarchal mentality are subtle, others are truly gruesome – the practice of dowry harassment, domestic violence, physical assault and violence against women are still so prevalent in our country, it is disheartening how unsafe the daughters of India feel in their own homeland. All of this directly has an impact on the health status of the women in our country. Consider this practice: traditionally, women are expected to cook and first serve food to the other household members – their husbands, in-laws and children – and even though it is not an explicit rule, they are usually the last ones to eat in the family.

In impoverished settings, where resources are limited, this also implies that women eat the least out of other members of the house. This manifests in the form of nutrition deficiencies in our girls. Government figures show that the prevalence of iron deficiency anaemia is over 60% amongst adolescent girls, which continues into adulthood and is a serious morbidity during pregnancy, making them susceptible to post-partum hemorrhage. Similarly, intimate partner violence during pregnancy directly impacts the health of the mother, thus threatening the birth outcome. Maternal nutrition significantly affects the nutrition of the baby, and increases the likelihood of a small and vulnerable neonate. Family planning and spacing between children, which is ideally supposed to be a discussion between partners, is still predominantly controlled by husbands in India. Modern methods of contraception are still only marginally used in India, and concentrated in urban parts of the country. Refusal by the husband to use condoms or purchasing contraceptive pills is so prevalent that unsurprisingly, hysterectomies are the most widely used form of family planning in India – only way women can exercise some agency over family planning. In states like Rajasthan and Bihar, at least one in ten pregnancies occur among teen mothers, contributing to a concomitant proportion of high-risk pregnancies in these states. The unifying subtext in all these social evils is a lack of bodily autonomy for women and limited decision making power to control their own health outcomes. This needs to change. In order for long-term change to happen, I believe it is essential to bring about equality in real terms – by breaking social norms that deny girls access to this autonomy, education, and a life where they can contribute to society at their true potential.

The government started the excellent initiative of *Beti Bachao Beti Padhao*. Over the last two decades, we have also made strides in improving India's maternal mortality rate, and improving obstetric service delivery across public hospitals in the country. Similarly, more can be done to ensure girls claim public spaces and do not allow them to become male dominated. One such avenue is to plan city and village infrastructure such that there are exclusive spaces for them to get together for physical activity. Unwanted male gaze pushes girls away from gyms and sports, which is pitiable. Globally, around 85% of girls

do not meet the WHO recommendations of at least 60 minutes per day of moderate to vigorous physical activity. This too contributes to their poor health status.

Health providers, especially in public hospitals, also have tremendous power in situations of abuse or assault. The culture of victim-blaming and shaming needs to stop. A little empathy can go a long way in protecting the future of a girl in physical danger. Girls and women need to trust their care providers to be able to confide in them and feel like they are in a safe space. Lastly, all of us, during our Sankalp Sampoorna Swasthya (SSS) visits, should encourage school teachers to talk about these difficult topics, counselling boys on the harsh realities of the world and to distinguish between right and wrong behavior. Children learn from what they see around them, and early counselling is the only way to ensure that we make social change with every succeeding generation. I do believe that in order to right the historical wrongs, it is men and boys who need to lead this change by example.

UPCOMING SECTIONS

Ethisection

Ethics in patient care and research is being increasingly recognized as an integral aspect of the medical profession. However, there remains considerable variation in the interpretation, acceptance and integration of ethical principles into day-to-day clinical practice. This section presents deliberations of situations that illustrate challenging ethical considerations in patient care, research or administration. The aim is to stimulate reflection using illustrative cases to understand the varied ethical perspectives, dilemmas faced and provide a balanced view point.

The article should be structured as a brief introduction, an illustrative case(s) followed by an analysis of the ethical issues involved through two or three commentaries, outcome of the case and a concluding paragraph providing a balanced ethical viewpoint. The case should highlight an ethical dilemma encountered in clinical practice, research or administrative set up. Some examples of cases that can be studied include issues related to inclusion of children from low- and middle-income countries (LMICs) as participants in funded clinical trials, triage in disasters, pediatric organ donation and transplantation, teenage pregnancy, prenatal counselling in genetic syndromes, disclosure of medical information to parents, etc. The case should be presented as a situational narrative in about 300-400 words. The privacy and confidentiality of the patient(s) must be maintained. The case is to be followed by a commentary of about 800-1000 words by 2-3 authors (pediatrician, resident doctor, nurse, ethicist, medical hospitalist, social worker, lawyer) who should be from different specialties/disciplines/with different administrative roles; a legal perspective should be preferably included. The article may present only one viewpoint or present an argument between two different perspectives which may be valid in different situations. The commentary is followed by a brief description of the outcome of the case, and the learning points from the case presented as conclusion (by the lead authors/ ethics expert). The total word count should not exceed 2500 words with a maximum of 10 references. A total of four authors is permitted. An unstructured abstract of about 200 words with a brief case summary and the ethical issue as a question should be included with 3-5 keywords.

This section will normally include articles by invitation. However, unsolicited articles are occasionally considered. Prospective authors can contact the editor about the suitability of their ethical dilemma by sending an email to jiap@iapindia.org. Authors are encouraged to avoid topics that have already been covered in previous issues in this section.

Beyond Borders

This section aims at featuring ideas from around the world that can inspire and guide efforts to create uniformity in healthcare standards globally. A perspective of about 1800 words is invited from public health experts to highlight the concerns in healthcare of children outside India attributed to region-specific problems like war, climate change, migrant population, cultural practices, and poverty. This section explores not only the barriers in healthcare but also provides promising solutions to help decrease the inequity in health.

The article should include a brief introduction which describes the origin of the problem (500 words) which is followed by a situational analysis highlighting the challenges and barriers contributing to the problem and the possible way forward (1000 words), and should end with a concluding paragraph of about 300 words. A maximum of three authors are permitted for this section. An unstructured abstract of about 200 words with 3-5 keywords, highlighting the region-specific problem, challenges and prospective solutions should be provided.

Child Health Technology

This section highlights innovations, inventions, pioneering research, or technological advancements in child health, which are likely to shape the future of child health. The aim is to apprise the readers about the technological breakthroughs in diagnosis and treatment of various diseases. This section includes a commentary of about 1200 words describing the technological advancement, progress made in India including its availability and accessibility, implications for patients and the roadmap ahead.

INVITED COMMENTARY

The Importance of Managing Acute Pain in the Neonatal Intensive Care Unit Context

HALEH HASHEMI, ESTREYA COHEN, REBECCA PILLAI RIDDELL*
Department of Psychology, York University, Toronto, ON, Canada.
**rpr@yorku.ca*

The significance of infant pain has evolved dramatically over the last few decades. Fifty years ago, it was common practice during infant surgeries to use paralytic drugs instead of anesthetics, grounded in the incorrect assumption that infants were incapable of experiencing pain [1]. This practice persisted until the combined efforts of pioneering basic and clinical researchers, alongside parental outcry, catalyzed a shift towards the acceptance of pain in infants. Scientific evidence confirmed that neonates possessed the anatomical and neurophysiological systems essential for pain perception, demonstrated both in animal and human subjects [2]. The history of incredulous neglect of infant pain underscores the importance of the present randomized control trial by Devi, et al. [3]. Early exposure to repetitive pain and distress has profound implications for brain development, pain processing, and stress response. Preterm infants in neonatal intensive care units (NICU), approximately 10% of all infants born globally [4], frequently endure between 12-17 painful procedures a day [5].

Experiencing pain in the NICU holds far-reaching implications, profoundly impacting the health and biopsychosocial development of premature infants [6]. Prolonged or recurrent pain during this crucial phase can disrupt neurodevelopment, potentially leading to cognitive, emo-tional, and behavioral challenges later in life. Physiological responses, including altered heart rate, blood pressure, and hormonal levels, can disrupt body systems. In addition, heightened pain sensitivity may endure, influencing pain perception throughout childhood and beyond. Moreover, the stress of NICU-related pain can dysregulate an infant's stress response system, impacting stress management and emotio-nal well-being [6]. These effects extend to behaviors like irritability, disrupted sleep, feeding difficulties, and strained parent-infant interactions. Importantly, unaddressed pain might also contribute to other chronic health conditions such as respiratory issues, further underscoring the urgency of evidence-based pain assessment and management in the NICU for short-term and long-term well-being [7].This concern gains particular significance in light of research which delves into the nuanced aspect of 'iatrogenically prolonged' pain experiences stemming from repetitive medical procedures in the NICU [8-10]. The cumulative burden of these interventions must be acknowledged [11], and may be a distinct pain state whereby the infant is 'chroni-cally pained' through a continuing barrage of acutely painful procedures before having resolved the pain from the last acutely painful procedure. These implications under-score the importance of mitigating the effects of both acute and prolonged pain for the overall health trajectory of preterm neonates [8]. One of the most common repetitive acutely painful procedures for infants in the NICU is the heel prick procedure.

Included in this issue of *Indian Pediatrics* is a randomized controlled trial [3] comparing neonatal procedural pain response across various heel prick devices. This article provides valuable insight into blood draw procedures in the NICU, by assessing pain responses in 180 clinically stable, non-ventilated neonates randomized to either an automatic lancet, a manual lancet, and a 26-gauge hypodermic needle. The heel pricks were conducted with reduced light and noise, and having oral dextrose administered 2-minutes prior to the prick as per standard of care. The authors concluded that the three devices elicit similar pain responses (using the well-validated Premature Infant Pain Profile-Revised); however, the use of hypodermic needles led to a higher number of painful squeezes during the procedure and longer cerebral oxygenation normalization time. This was contrary to other findings in the literature, which demonstrated a clear superiority for the automatic lancet, over both manual lancet and needle for heel pricks. Notable structural differences with the lancing instruments available within India were noted as a mitigating factor. Another notable feature of the article was the use cerebral oxygenation as an outcome measure showing that needles were less optimal. This article draws our attention on an important aspect of pain management – procedural interventions that can reduce the pain burden. It serves as a reminder to clinicians to think about the multifaceted ways to manage pain.

Within the 5Ps of pain management (physical, pharmacological, procedural, psychological, and process) [7], discovering and utilizing the least painful tools is a critical procedural component to contemplate [3]. In addition, to pharmacological strategies such as sweetening agents and topical anesthetics, there are an abundance of no-cost non-pharmacological interventions that have been shown to support infant pain management in the NICU. The 2023 Cochrane Review on non-pharmacological strategies for managing infant and young child procedural pain reviews 138 studies examining 24 separate techniques. While 12 strategies were focused specifically on preterm infants and most showed evidence of moderating pain, the unfortunate situation is that not one strategy is backed with a 'high certainty' in the evidence because of the rampant challenge of bias in trials due to methodological concerns (or in the older literatures, poor reporting of methodology) [9]. Nonetheless, non-pharmacological strategies are critical due to the frequency of acutely painful procedures experienced in the NICU. Given the low/no-cost of these strategies and possibility to utilize parent caregivers in these strategies (e.g., skin-to-skin care, facilitated tucking, non-nutritive sucking) these approaches should be prioritized, particularly in low-resource medical environments. The current article's content and quality contribute to a much-needed body of lower-risk of bias literature on procedural pain in neonates [3].

The significance of neonatal pain needs to be reflected in an appropriate body of high-quality research on measures and practices to protect their wellbeing. Through the generation and integration of clinically relevant pain research on NICU pain, such as the present trial [3], the impact of repeated painful procedures can become moderated to better optimize the development and well-being of vulnerable preterm infants.

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PERSPECTIVE

Puberty and Bone Health in Chronic Disease

MARGARET ZACHARIN

Department of Endocrinology, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia.

Correspondence to: Dr Margaret Zacharin, Department of Endocrinology, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia. margaret.zacharin@rch.org.au

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Linear growth, onset of and progress through puberty are all adversely affected by chronic diseases during childhood and adolescence. Peak bone mass accrual by the end of adolescence determines adult fracture risk. Given that half of total lifetime bone mass is accrued during the pubertal years under the influence of sex hormones, normal timing of pubertal onset, with attention to completion of feminization for girls or virilization in boys is integral to achievement of optimal bone mass, which in turn will reduce adult fracture risk for those who have a chronic relapsing, remitting or persistent illness.

Key words: *Adolescence, Disability, Low bone mass, Osteoporosis, Vitamin D*.

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A broad range of chronic illnesses and diseases occurring during childhood and adolescence may affect linear growth, time of pubertal onset, progression through puberty, and bone mass accrual. These include genetic disorders, cerebral palsy, malabsorption, and malignancy, chronic musculoskeletal, autoimmune and other inflammatory conditions [1-5]. Medical treatments specific to these conditions may also adversely affect growth and puberty [4].

Non-communicable diseases now comprise more than 60% of all childhood and adolescent illness in the developing world, with changes in the pattern of diseases in recent years [6]. Up to 30 times increase in inflammatory bowel disease has been reported worldwide [2]. Longevity has increased, such that young people with cystic fibrosis, disability and muscular dystrophies are surviving well into adulthood. More than 80% of those with childhood cancers now survive [7]. Thus, there is a need to monitor and optimize growth and puberty, for physical and psychosocial benefits to the adolescent and to reduce the impact of ongoing, recurrent or new adult health challenges [4].

Nutritional deficiencies, malabsorption, bowel losses, pro-inflammatory cytokines, variations in leptin, serotonin and insulin like growth factor (IGF1), plus reduced gene expression of steroidogenic enzymes all have adverse effects on growth, with down-regulation of the hypothalamic pituitary gonadal (HPG) axis, suppression of gonadotropin releasing hormone (GnRH) synthesis, gonadotropin release and gonadal steroid biosynthesis contributing to both growth failure and reduced bone mass [8].

Impaired pubertal bone mass acquisition reduces peak bone mass and increases adult osteoporosis risk. Causative factors vary, depending upon the type of chronic condition as well as treatment modalities used for control. Increased osteoclast activity and reduced osteoblast function with high dose, long-term or repeated use of glucocorticoids or anticonvulsants, contribute to impairment of cortical bone accrual and trabecular mineralization. Reduced weight bearing and impaired musculature, with limitation of stability and increased risk of falls, cumulatively increase appendicular skeletal fracture risk. Glucocorticoids cause growth failure in chronic disease via complex mechanisms of inhibition of adrenal hormone production (DHEAS), leading to pubertal delay, reduced growth hormone release and IGF-bioactivity, reduced chondrogenesis via less collagen synthesis [8,9]. Epiphyseal destruction in some inflammatory disorders has a compounding effect on poor adult height prognosis [1].

A multidisciplinary assessment is crucial to optimize management of the underlying disorder, if successful pubertal and bone health outcomes are to be achieved [8-10]. The use of newer therapeutic agents has changed the pattern of disease activity in many conditions, including chronic inflammatory disorders and cancers. However, many of these agents are costly and currently inaccessible to many institutions and families [11,12]. Glucocorticoids remain the mainstay of treatment for many conditions, with proven benefits but at the expense of serious adverse effects on growth, puberty and bone health.

To deliver effective interventions, aiming to reduce the cumulative adverse effects on growth and puberty, an

understanding of normal determinants of bone mass accrual and the pubertal cascade is essential. Bone mass increases throughout childhood. During adolescence, sex hormones have a differential effect on bone size. Estrogen inhibits periosteal apposition of bone, stimulates endocortical formation, leading to narrowing of the medullary cavity. In boys, testosterone increases bone size by apposition of bone on the exterior surface and increase in the distance of the cortex from the neutral axis. This difference accounts for the reduced adult fracture risk in adult males, due to a larger, more stable overall bone size, although the rate of bone loss with any chronic disease or its treatment is the same for both sexes.

The determinants of bone strength include structural components of load, geometry and mineral deposition. During chronic illness and/or immobilization, weight-bearing is reduced, muscle load decreases and calcium loss increases, resulting in smaller, more fragile bones.

OPTIMIZING BONE HEALTH IN CHILDREN WITH CHRONIC DISEASES

Assessment

The most important starting point for evaluation requires a pediatrician to have an in depth understanding of the tools used for assessment, to measure the degree of deficit, and to document effect of an intervention. Standard bone density assessment compares a child to age- and sex-matched controls but does not adjust for height or pubertal status. It is essential to adjust for height for interpretation. Various calculations are available for this purpose. Regardless of height, using the child or adolescent as his or her own control provides the best reference for repeated measurements over time. The normal rate of bone mass accrual prior to puberty is around 2-5% per annum, increasing to 10-15% during puberty. Almost half of total bone mass for life is accumulated during puberty in females, with slightly less in males [13]. Failure to achieve an annual increase in bone mass indicates a need to intervene. For conditions of potential extreme bone fragility, peripheral quantitative computer tomography (pQCT), if available, can be used for cortical bone assessment .

Puberty should follow a well-defined cascade in both sexes, in girls, with onset between ages 8-13 years with breast development, accompanied by early linear growth acceleration, proceding to menstruation after 2.5-3 years; and in males, with onset between 9-14 years, with testicular enlargement, followed by virilization and a later growth spurt. These trajectories must be observed, or mimicked with treatment, if a child with a chronic disease is to achieve optimal height and adult bone mass [10]. Regular assessment to ensure whether pubertal progress is taking place will help in defining the need for endocrine referral. Pubertal induction and support, through to adult feminization or masculinization may need to be considered in all chronic disease conditions. Unfortunately, evaluation of these essential processes is frequently missed during clinical follow-up due to constraints of time, regularity of attendance and urgent medical needs that appear to be more demanding. Some times, there is lack of knowledge of the primary physician regarding pubertal induction and its importance

Interventions

To obtain efficient linear growth and bone mass accrual, efforts should first be directed towards achievement of best possible control of the underlying disorder, taking a window of opportunity when health is best and medications are minimal, to achieve maximal effect of any intervention.

Nutrition: Adequate nutrititional support may require the services of a dietitian. Sufficient calcium and vitamin D are essential for bone development. Poor absorption and impaired metabolism in the presence of glucocorticoids require increased dosing of both calcium and vitamin D.

Pubertal induction: This should be considered by age 12-13 years for girls and by age 14 in boys, with appropriate endocrine referral if puberty has not commenced, or if there is evidence of pubertal arrest. Medication choice may be based on availability and personal preference of the patient. In principle, transdermal oestrogen or testosterone would be the preferred choice of hormone replacement (HRT) in the presence of malabsorption. A slowly increasing regime should be used over 2-3 years, to mimic the normal pubertal trajectory. HRT should be continued until epiphyseal fusion has been achieved, then treatment may be withdrawn, with reassessment to see if the adolescent can maintain independent hormonal status. [14].

Adolescents, who would benefit from intervention, include:

Chronic inflammatory conditions (*e.g., inflammatory bowel disease, juvenile arthritis*): Transdermal estrogen is theoretically preferred due to potential for impaired or erratic absorption. Due to unpredictable relapsing -remitting nature of the conditions, it is usually better to complete puberty and linear growth until epiphyseal fusion before re-assessment, as outlined above.

Nutritional deficit: Consideration for supportive HRT for girls with established eating disorders may be effective to improve bone mass accrual, feminization and improved psychologic outlook. Again, transdermal oestrogen is more effective and more likely to be acceptable to this group.

Musculoskeletal disorders: Using this regimen of pubertal HRT support, we have demonstrated effective increase in

bone mass, of nearly 25% at lumbar spine over 2-3 years in boys with Duchenne muscular dystrophy, despite the necessity for maintenance high dose, chronic glucocorticoid, underlining a remarkable replication of normal physiology even under extremely adverse circumstances [15].

Adult evidence suggests that up to 50% of young adults with cerebral palsy and associated disorders cannot maintain adequate level of sex hormones, due to poor health, with or without midline abnormalities associated with hypothalamic pituitary dysfunction. Ongoing surveillance is therefore required in this group [16-19].

After cancer treatment: For the specific case of a child who has chronic nutritional insufficiency after chemotherapy for malignant disease, the use of cyproheptadine can increase appetite and reduce vomiting, as an adjunct to care in the early months of recovery [20].

Other Considerations and Interventions

- Targeted bone therapies of bisphosphonate, sclerostin antibody or RANKL inhibitor should be limited to cases where there is evidence of inexorable continuing bone loss and /or vertebral fracture despite the above measures [21,22].
- In those who require ongoing exposure to glucocorticoids, where there is evidence of Cushingoid features and growth failure, the glucocorticoid can be assumed to be causing rapid bone loss. However, if malabsorption is severe, cushingoid features may be absent. Vertebral fractures are usually asymptomatic in children and adolescents and will only be detected if suitable imaging is undertaken, with either lateral vertebral morphometry or with a lateral thoraco-lumbar spine *X*-ray.
- Weight-bearing, even for limited periods daily, and biomechanical stimulation have been shown to be of benefit for bone mass accrual in those with a disability, but access to the latter is frequently limited by equipment availability and cost. For those with a major disability, where the young person is non-weight bearing, both sex homone replacement and bone targeted treatments have been shown to increase bone mass However, lack of muscle mass, risk for falls, inability to undertake evasive action in case of falls, together with smaller appendicular skeletal size, contribute to a degree of unavoidable fracture risk. Family understanding of this issue is imperative to avoid disappointment with therapeutic modalities and to enable continued professional engagement for attention, where needed.

CONCLUSIONS

In all forms of chronic disease, attention should be directed towards completion of normal physiologic processes, risk reduction, prevention of future deterioration and loss of function, together with transmission of sufficient knowledge to the family and carers, to facilitate understanding of on-going and future needs. Regular surveillance is needed to identify problems and to plan a suitable course of action.

Attending pediatricians and physicians must be familiar with recent, evidence-based recommendations and should refer their patients for timely endocrine assessment. Transmission of appropriate information regarding endocrine needs is also paramount for future medical staff to facilitate action. Long-term follow-up and transition information is essential to maintain gains and to prevent deterioration.

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RESEARCH PAPER

Neonatal Pain Response to Various Heel Prick Devices: A Randomized Controlled Trial

RISHA DEVI, MAYANK PRIYADARSHI, POONAM SINGH, SUMAN CHAURASIA, SRIPARNA BASU

Department of Neonatology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand.

Correspondence to: Prof Sriparna Basu, Professor and Head, Department of Neonatology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand 249 203. sriparna.neonat@aiimsrishikesh.edu.in

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Background: Heel prick is a commonly performed painful intervention in neonates. Though different devices are available, there is a need to compare the procedural pain response elicited by them.

Objectives: To compare the neonatal pain response to three different heel prick devices; automatic lancet, manual lancet, and 26-gauge (G) hypodermic needle.

Design: Parallel-group three-arm randomized controlled trial.

Participants: Clinically stable neonates of gestational age >28 weeks and birth weight >800 g undergoing heel prick for estimation of random blood sugar.

Methods: One hundred and eighty neonates were randomized to automatic lancet (*n*=59), manual lancet (*n*=59), or needle (*n*=62) groups between March, 2021 and August, 2022. The primary outcome was the premature infant pain profile-revised (PIPP-R) score. Secondary outcomes were post-intervention cerebral regional oxygen saturation (CrSO2), changes in CrSO2 (ΔCrSO2), the time for CrSO2 normalization using near-infrared spectroscopy, duration of audible cry, and the number of squeezes and pricks needed. Intention-to-treat analysis was done.

Results: Median (IQR) of PIPP-R scores were comparable in the automatic lancet [6 (4, 7.5)], manual lancet [5.5 (3.5, 8)], and needle [6 (3-9.6)] groups; *P*=0.59. No difference was observed in post-intervention CrSO2, ΔCrSO2, and the number of pricks. However, the time required for CrSO2 normalization and the number of squeezes were significantly higher with the needle.

Conclusions: All three devices induced similar pain responses to heel prick in neonates; though, the number of squeezes needed was higher with the needle.

Keywords: *Automatic lancet, Blood sampling, Manual lancet, Needle*.

Trial registration: Clinical Trial Registry of India: No. CTRI/2021/03/031863.

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Neonates are frequently exposed to multiple painful procedures, both as a part of routine care protocol as well as intensive care management policies [1-3]. Repeated painful stimuli during the neonatal period are often associated with neurosensory and cognitive impairment in later life [4-6]. The heel prick is one of the most frequently performed painful interventions in neonatal intensive care units (NICUs). Common devices available for heel pricks include an automatic lancet, manual lancet, and hypodermic needles. Automatic lancets are the recommended device, as the device-related adverse effects such as pain, need for repeated pricks, and deep tissue injury are less [7-11]. However, lower-middle-income countries (LMICs) continue to use manual lancets and hypodermic needles due to their low cost and easy availability.

The Premature infant pain profile-revised (PIPP-R) scale is one of the most frequently used objective scoring systems to measure pain response in neonates [12,13]. However, the PIPP-R score evaluates behavioral and physiological aspects of pain response and lacks the ability to detect pain perception at the cortical level [14]. On the other hand, neurophysiological measurements have shown a better temporal and spatial association with pain-mediated cortical activation [13,15]. Nociceptive responses in somatosensory areas of the brain are reflected by an alteration in regional cerebral oxygen saturation ($CrSO_2$) that can be quantified non-invasively by near-infrared spectroscopy (NIRS) [16]. NIRS has also shown a significant correlation with the PIPP-R scale [17].

Though, a few previous studies have compared pain scores to different heel prick devices [9,18], evidence from LMICs is limited [19]. The present study assessed the neonatal pain response to different heel prick devices viz., automatic lancet, manual lancet, and 26-gauge (G) hypodermic needle. We hypothesized that the pain score would be lower with the use of an automatic or manual lancet compared to a 26G hypodermic needle.

METHODS

This parallel-group, three-arm randomized controlled trial (RCT) was conducted over 17 months (March, 2021 to August, 2022) after obtaining approval from the institutional ethics committee. The trial was registered with the Clinical

Trial Registry of India. Written informed consent in the local language was taken from the parents before enrollment.

Settings and study population: The present study was conducted at a level-III NICU. Neonates of gestational age >28 weeks and birth weight >800 g, stable on room air without any respiratory support, who required clinically indicated heel prick for random blood sugar assessment in the first week of life were included in the study. Each neonate was enrolled only once. Exclusion criteria included the presence of major congenital malformations, hemodynamic instability/shock, hemodynamically-significant patent ductus arteriosus, perinatal asphyxia with hypoxic-ischemic encephalopathy, major intraventricular hemorrhage (grade III/IV) or periventricular leukomalacia, the requirement of respiratory support, sedation or analgesia, and a major painful procedure done in the preceding 24 hours.

The primary outcome was the PIPP-R score [20] measured during the heel prick. The secondary outcomes included changes in cerebral regional oxygen saturation (ΔCrSO2), CrSO2 normalization time (time to reach baseline value), duration of audible cry, number of squeezes and pricks required for sample collection, and correlation of CrSO2 values with PIPP-R scores.

Randomization, group allocation, and blinding: An independent statistician, not involved in the study, generated a computer-based variable-block size random sequence (*http://www.sealedenvelope.com*) in order to randomly assign the neonates into one of the three puncture device groups viz., automated lancet, manual lancet, and 26G hypodermic needle in the ratio of 1:1:1. Randomization was stratified into two gestation-based subgroups: 28^{+0} weeks to 33^{+6} weeks, and ≥34 weeks. Parental consent was taken at the time of recruitment of an eligible neonate. Allocation concealment was ensured using sequentially numbered sealed and opaque envelopes. All three devices were kept ready at the bedside of the neonate, and the envelope for the stratified group was opened immediately before the procedure to reveal the allocated intervention. The treating physicians were not blinded due to the nature of the trial, while the outcome assessors and the statistician were blinded regarding the group allocation of the neonate.

Intervention: The heel prick was performed by automatic lancet (Accu-Chek Safe-T-Pro UNO), manual lancet (28G round lancet, Dr. Safe, Safe Lancet Engg Pvt. Ltd.), or needle, (26G Dispovan disposable needle) when clinically indicated. It was ensured that no painful intervention was done in the hours prior to the heel prick, the neonates had been fed 1-1½ hours before, and other activities like diaper changes were done at least 30 minutes before the procedure. A developmentally supportive environment with reduced light and noise was ensured during the heel prick. Dextrose 25% (in weight-specific dose) was instilled orally two minutes prior to the prick according to the pain management protocol of our NICU.

The cerebral neonatal sensor of NIRS (INVOS 5100C cerebral/somatic oximeter, Medtronics) was secured to the forehead and Masimo Rad-97 pulse oximeter probe was attached to the right hand, 10 minutes prior to the prick. The head position was kept in the midline. The prick was performed on the pre-identified site without any local infection or injury on the lateral or medial side of the heel. The site was ensured to be warm, cleansed with a 70% alcohol swab, and air-dried before pricking. Only a drop of blood sufficient for random blood sugar assessment was collected.

Videotaping of the entire procedure was done. The recording was initiated 5 minutes prior to the heel prick and ended 5 minutes after the heel prick. The baseline parameters were documented 15 seconds prior to the preparation of the skin. The assessment of pain response was done 0-30 seconds after the heel prick. Video recordings included the facial expressions of the neonate and the displays of the NIRS and the pulse oximeter. No part of the intervention was included in the recording and no verbal mention of the heel prick device used was done during videotaping to ensure the blinding of the assessor.

The video clips were scrutinized to retrieve pertinent data including baseline behavioral state and vital parameters of the neonate. Baseline CrSO2, the time to its normalization, and the duration of crying were also noted. Later, PIPP-R scoring was performed by two independent assessors from the video recordings. ΔCrSO2 was calculated from video recordings using the baseline CrSO2 and the lowest CrSO2 observed during 30 seconds following the prick.

As no previous study has compared pain scores after heel prick with a needle vs both manual and automatic lancets, our sample size was based on the study of Britto, et al. [19], where a comparison was made between needle and manual lancet. Assuming a similar mean PIPP-R of 10 in neonates in the 26G needle group and 8 in the automatic or manual lancet group, a sample size of 54 neonates was calculated for each group with a power of 80% and a significance level of 5% (*http://www.sealedenvelope.com*). With an expected attrition of 10%, a total sample size of 180 (60 in each group) was calculated.

Statistical analysis: Microsoft Excel 2019 was used to collate the data sets and SPSS version 25.0 (IBM Corp) was used for an intention-to-treat analysis. Categorical measurements were expressed as percentages and continuous variables were expressed as mean (SD) or median (IQR). Fisher exact test or the Chi-square test was used to compare

categorical variables. One-way analysis of variance (ANOVA) or Kruskal-Wallis test was used to compare continuous variables with post hoc Bonferroni or Dunn test, as appropriate. Subgroup analysis was done as per gestational age stratification. Multiple linear regression was used to evaluate the effect of intervention and related factors on PIPP-R score. The Pearson correlation coefficient was calculated to assess the correlation. Inter-rater reliability was assessed by the calculation of the intra-class correlation coefficient. A *P* value <0.05 was considered statistically significant.

RESULTS

A total of 234 neonates, requiring heel lance during the study period, were assessed for inclusion in the trial. After exclusions, 180 neonates were randomized to receive heel lance by automatic lancet (*n*=59), manual lancet (*n*=59), or 26G needle (*n*=62). All the participants received the allocated intervention and were analyzed for the primary outcome (**Fig. 1**). There was no protocol deviation.

All three groups were comparable with respect to maternal variables and birth weight, gestational age, Apgar score, gender, intrauterine growth status, and postmenstrual and postnatal age at heel prick. Median (IQR) gestational age in the automatic lancet, manual lancet, and needle groups were 35.3 (33.7-36.6), 35.6 (33.2-38), and 36.4 (33.9-38.1) weeks, respectively. Other baseline physiological parameters were also comparable among the groups (**Table I**).

Median (IQR) of the averaged PIPP-R scores rated by two assessors, evaluated 0-30 seconds from the heel-prick, were comparable among the automatic lancet [6 (4-7.5)], manual lancet [5.5 (3.5-8)], and needle [6 (3-9.6)] groups (*P*=0.59) (**Table II**). No inter-group difference was observed in the gestational age-based subgroup analysis. On multiple linear regression, PIPP-R scores remained comparable among the three intervention groups despite physiological variability including gestational age, birth weight, and intrauterine growth status (**Web Table I**).

There was no difference in post-intervention CrSO2 and ΔCrSO2 among the three groups even after gestational age stratification. The duration of audible cry and the number of pricks needed for sample collection were comparable in all three groups. The time taken for CrSO2 values to normalize and the number of squeezes to obtain blood samples were

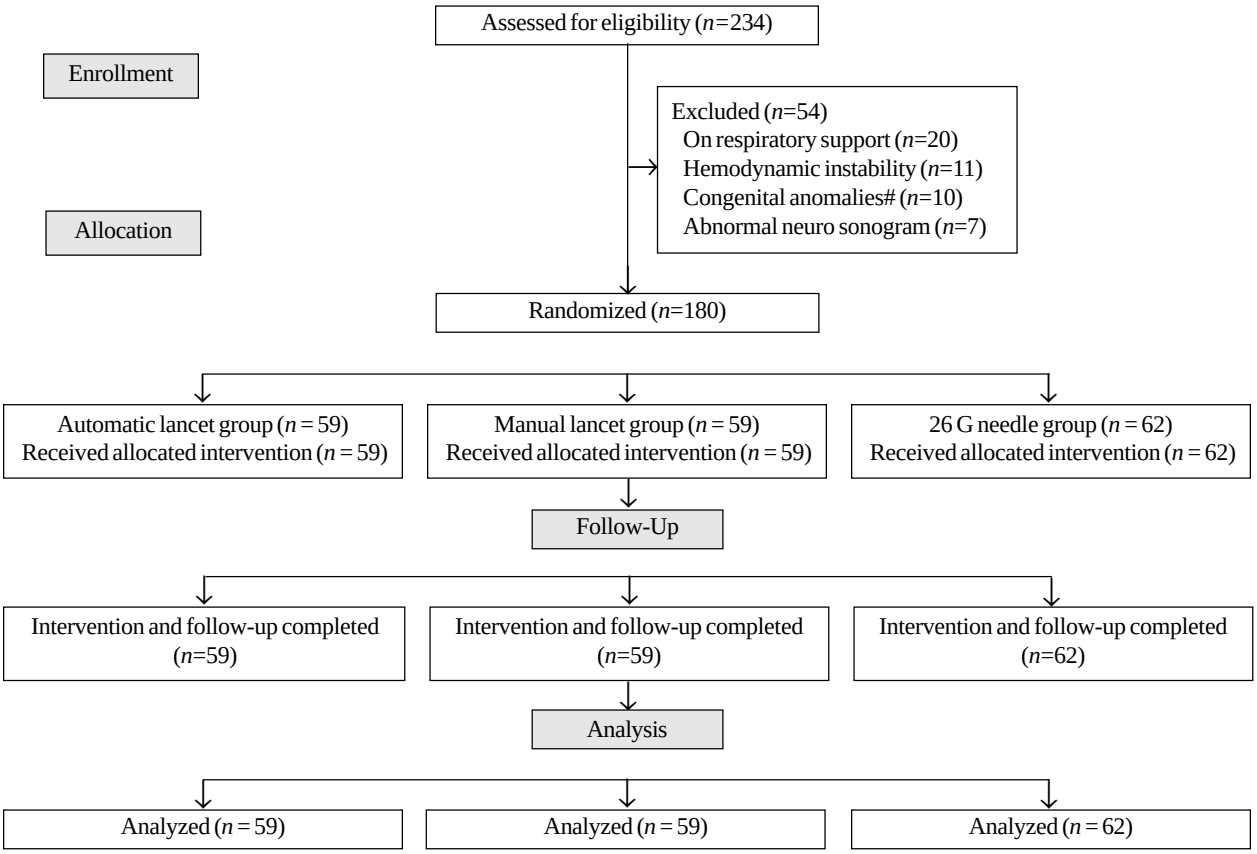

Fig. 1 Study flow diagram.

Table I Baseline Characteristics of the Enrolled Neonates

Characteristics	*Automatic lancet (n=59)*	*Manual lancet (n=59)*	*Needle (n=62)*
Maternal characteristics			
Anemia (Hb <11.0 g/dL)	33 (55.9)	36 (61.0)	35 (56.5)
Pre-eclampsia/eclampsia	8 (13.6)	10 (15.3)	7 (11.3)
Antepartum hemorrhage	3 (5.1)	2 (3.3)	2 (3.2)
Cesarean delivery	36 (61.0)	34 (57.6)	37 (59.6)
General anesthesia	3 (5.1)	2 (3.4)	3 (4.8)
Received of magnesium sulfate	5 (8.5)	6 (10.2)	4 (6.5)
Neonatal characteristics			
Male	26 (44)	28 (48)	30 (48)
Birth weight (g)[c]			
1000-1499	10 (17)	12 (20)	8 (13)
1500-2499	39 (66)	29 (49)	33 (53)
≥2500	10 (17)	18 (31)	20 (32)
Gestational age (wk)			
28-31	5 (8)	7 (12)	7 (11)
32-33	13 (22)	14 (24)	9 (15)
34-36	28 (48)	16 (27)	21 (34)
37-42	13 (22)	22 (37)	25 (40)
Small for gestational age	27 (46)	26 (44)	30 (48)
Apgar score[b]			
1 min	9 (8,9)	9 (8,9)	9 (8,9)
5 min	9 (9,9)	9 (9,9)	9 (9,9)
Postnatal age (h)[b]	23 (19,49)	27 (20,49)	28 (19,60)
Baseline physiological parameters[a]			
Heart rate (beats/min)	150 (18)	148 (18)	144 (17)
Peripheral oxygen saturation (%)	95.1 (2.7)	94.9 (2.9)	95.3 (2.9)
Cerebral regional oxygen saturation (%)	80.5 (8.6)	77.5 (8.9)	78.9 (7.7)

Hemoglobin (Hb); Values in no. (%), [a]mean (SD) or [b]median (IQR); [c]One neonate in needle group had birthweight of <1000 g. P>0.05 for all comparisons.

significantly higher with the use of needles (**Table III**). ΔCrSO2 correlated significantly with the overall PIPP-R score, its facial score component, and the duration of audible cry, though, the strength of association was poor (**Web Table II**). The intra-class correlation coefficient (95% CI) for the assessment of PIPP-R scoring was 0.92 (0.89-0.94).

DISCUSSION

The present RCT assessed the neonatal pain response to three different heel prick devices. There was no significant difference in the PIPP-R scores with the use of the automatic lancet, manual lancet, and 26G needle. Post-intervention CrSO2 levels, ΔCrSO2, duration of audible cry, and the number of pricks were comparable among the three heel prick devices.

Some of the previous trials have compared automatic vs manual lancets for the estimation of neonatal pain response during heel prick [7,18], while several others have compared lancets vs needles [9,19]. Most of the trials have assessed pain with PIPP or Neonatal Infant Pain Scale, NIPS [7,9,18,19] whereas some have reported CrSO2 as well [7,17].

Both the trials that compared the neonatal pain response to automatic vs manual lancets documented the superiority of the automatic device in terms of lesser pain scores [7,18], smaller duration of an audible cry [18], and decreased need for repeated punctures and squeezes [7]. The difference in results in our study could be the use of cut-type automatic lancets that have a smaller penetration depth but wider incision (1 mm penetration depth and 2.5 mm width) in these studies, while we have used a needle-shaped puncture-type (1.5 mm insertion depth and 0.36 mm width) automatic lancet available in India. This discrepancy in dimensions could have resulted in deeper penetration resulting in an incision/prick wound with an automatic lancet that was more painful [21]. Another recent trial compared pain response elicited by automatic lancets and needles during heel prick in neonates of birth weight ≥1,500 g and gestational age of ≥30 weeks using the NIPS score [9]. The authors documented a significantly lower NIPS score in the automatic lancet group compared to the needle, though the number of squeezes was similar. The difference in results could be due to the use of a thicker needle (23G) compared to ours (26G). Similarly, another trial conducted in India [19] compared manual lancets vs 26G needles for heel prick and the authors did not

Table II Premature Infant Pain Profile - Revised (PIPP-R) Scores in Neonates Undergoing Heel-Prick With Different Devices

Variables	*Automatic lancet*		*Manual lancet*		*Needle*		*P value*
	n	*Score*	*n*	*Score*	*n*	*Score*	
All neonates	59	6 (4, 7.5)	59	5.5 (3.5, 8)	62	6 (3, 9.6)	0.6
Gestational age 28-33 wk	18	5.8 (1.8, 8)	21	6 (4, 8)	16	8 (5, 10.8)	0.3
Gestational age ≥34 wk	47	6 (4, 8)	38	5.3 (2.9, 8.3)	46	5.5 (3, 8.4)	0.9

All values in median (IQR).

Table III Secondary Outcomes in Neonates Undergoing Heel Prick With Different Devices

Variables	*No.*	*Automatic lancet (n=59)*	*No.*	*Manual lancet (n=59)*	*No.*	*Needle (n=62)*
Post-intervention CrSO2 (%)[a]						
Overall	59	75.1 (8.8)	59	72.5 (9.8)	62	72.8 (8.5)
Gestational age 28 - 33 wk[a]	18	73.1 (10.7)	21	69.2 (11.4)	16	71.1 (9.6)
Gestational age ≥34 wk[a]	41	75.9 (7.9)	38	74.3 (8.4)	46	73.4 (8.2)
Change in CrSO2 (%)[b]						
Overall		4 (2, 7)		4 (2, 7)		6 (3, 9)
Gestational age 28 - 33 wk	18	3.5 (2, 6.3)	21	6 (2, 7.5)	16	5.5 (2.3, 8.8)
Gestational age ≥34 wk	41	4 (2, 8)	38	4 (2, 6)	46	6 (3, 9)
CrSO2 normalization time (s)[b,c,d]						
Overall		7 (2, 20)		7 (4, 16)		13 (6, 40)
Gestational age 28 - 33 wk	18	4 (0, 27.5)	21	10 (4, 18.5)	16	10 (5, 35)
Gestational age ≥34 wk	41	7 (5, 19.5)	*38*	7 (3.5, 16)	*46*	16 (7, 40)
Duration of audible cry (s)[b]	59	5 (0, 8)	59	2 (0, 7)	62	2.5 (0, 9)
Number of squeezes[b,d]	59	0 (0, 1)	59	0 (0, 1)	62	1 (0, 1)
Number of pricks[b]	59	1 (1, 1)	59	1 (1, 1)	62	1 (1, 1)

Values in no. (%), [a]mean (SD) or [b]median (IQR). CrSO2: cerebral regional oxygen saturation. [c]CrSO2 did not reach the baseline value in 1 neonate in automatic lancet, and 3 neonates in the needle group till the observation time. [d]P<0.05;

find any significant difference in the median PIPP score, though the duration of crying was less with lancets [19].

We did not find any significant difference in post-intervention CrSO2 and $\Delta CrSO_2$ among the groups, while a previous study [7] has documented a significant decrease during and after a puncture with a manual lancet but not with an automatic lancet. The inclusion of sick neonates in their study could be one of the reasons for this difference. Previous studies have shown a high correlation coefficient between the PIPP/PIPP-R scores and CrSO2 [13,17]. The poor association seen in this study could have been because of multiple parameters such as gestational and postnatal age, hemodynamic status, receipt of oxygen, and hematocrit [22].

The major strengths of the present study are a large sample size, a three-arm design, and a correlation of pain scores with cerebral oxygenation. The use of videography and their analysis by two different blinded assessors with a good inter-rater agreement was another strength. There are several limitations of this trial as well. Firstly, we have excluded extremely preterm neonates, as they remain mostly on respiratory support during the early days of life; though approximately one-third of the recruited neonates were early preterm. We have used a needle-shaped fully automatic lancet which is recognized as a more painful type, due to the non-availability of a puncture-type device. Moreover, we have not done a serial measurement of the PIPP-R score after the heel prick to observe any prolonged response to pain, although we have measured the duration of the cry. Lastly, we are not sure about the clinical implication of delayed normalization of CrSO2 in the needle group, as a long-term neurological follow-up was not included in the study.

All three devices evoked similar pain responses and ΔCrSO2 to heel prick in neonates, though CrSO2 normalization time and the number of squeezes were higher with the use of needles. Further studies are necessary to compare different devices for heel prick with long-term neurological follow-up.

Ethics clearance: Institute Ethics Committee, AIIMS, Rishikesh; No: AIIMS/IEC/21/100 dated Feb 12, 2021.
Contributors: RD: recruited patients, collected, and analyzed the data, and drafted the initial manuscript; SB, MP: supervised data collection and analysis of data and did critical revision and finalization of the manuscript; PS, SC: contributed to the study design, data analysis, and interpretation. All authors approved the final manuscript as submitted.
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A*vailability of data and material*: Individual de-identified participant data will be shared with researchers whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals should be directed to Dr. Risha Devi at e-mail *legenddevi@gmail.com* Data will be available beginning 9 months and ending 36 months following article publication.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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WHAT IS ALREADY KNOWN?

- Automatic lancets have been shown to cause less pain when compared to manual lancets or needles for neonatal heel-prick.

WHAT THIS STUDY ADDS?

- Automatic lancet, manual lancet, and hypodermic needles evoked similar pain responses and changes in cerebral oxygenation ($CrSO_2$) during heel prick in stable neonates. $CrSO_2$ normalization time and the number of squeezes were more with the use of needles.

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Web Table I Multiple Linear Regression Analysis for the Effect of Intervention and Related Factors on PIPP-R Scores in the Study Population

Factors	*Adjusted β (95% CI)*[a]	*P value*
Intervention group		
Automatic lancet	Ref	
Manual lancet	0.30 (-0.99, 1.60)	0.64
26G needle	0.82 (-0.47, 2.10)	0.21
Birth weight (g)	-0.0014 (-.0029, 0.0002)	0.08
Gestation (wk)	0.08 (-0.27, 0.43)	0.64
Male gender	-0.14 (-1.21, 0.93)	0.80
Intrauterine growth status	-1.03 (-2.35, 0.29)	0.12
Baseline heart rate	-0.017 (-0.05, 0.02)	0.32
Baseline oxygen saturation	0.22 (0.03, 0.41)	0.02
Baseline behavioral state	0.42 (-0.12, 0.97)	0.12

[a]*Beta coefficients derived from multiple linear regression after adjusting for intervention group, gestation, birth weight, gender, growth status, and baseline physiological variables (heart rate, saturation, and behavioral state).*

Web Table II Correlation of Various Pain Parameters with Cerebral Regional Oxygen Saturation

Parameter	*Pearson correlation coefficient (r)*	*P value*
Video assessed PIPP-R at 0-30 s	0.224	0.003
Facial expression score of PIPP-R	0.216	0.004
Heart rate score of PIPP-R	0.117	0.119
Oxygen saturation score of PIPP-R	0.089	0.235
Duration of audible cry	0.199	0.007

PIPP-R: Premature infant pain profile revised.

RESEARCH PAPER

Longitudinal Growth and Undernutrition Burden Among Term Low Birth Weight Newborns Reared in Adverse Socioeconomic Conditions in Delhi

MANPREET KAUR,[1] GEETA TRILOK-KUMAR,[2] SIKHA SINHA,[3] SUZANNE FILTEAU,[4] ANURA V KURPAD,[5] CLIVE OSMOND,[6] HARSHPAL SINGH SACHDEV[3]

[1]*Global Clinical Development Statistics and Data Management, Veterinary Medicine Research and Development, Zoetis, Zaventem, Belgium.*
[2]*Delhi School of Public Health, Delhi University, Delhi, India.*
[3]*Division of Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi, India.*
[4]*Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
[5]*Department of Physiology, St John's Medical College, Bengaluru, Karnataka, India.*
[6]*Biostatistics, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom.*
Correspondence to: Prof Harshpal Singh Sachdev, Senior Consultant, Department of Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, B-16 Qutab Institutional Area, New Delhi 110 016, India.
hpssachdev@gmail.com
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Background: There is limited data in term low birth weight neonates from urban poor settings on the incidence of and recovery from undernutrition and co-existence of its different forms, under conditions of appropriate health and nutrition care counselling.

Objectives: To determine the longitudinal growth and undernutrition burden among term low birth weight newborns reared in adverse conditions, but with appropriate counselling.

Methods: The study reports follow-up data from DIVIDS trial. 2079 term low birth weight (1800-2499 grams) newborns from an urban poor setting were followed-up for growth from 0 to 26 weeks (*n*=1282) and at 2.8-6.8 years (*n*=912). Using Cole LMS approach, age- and sex-specific internal *z* scores were computed and subsequently adjusted for the effect of a vitamin D intervention and potential bias due to attrition. Back-transformed measurements were then used to compute WHO *z* scores for height for age (HAZ), weight for age (WAZ), and BMI for age (BMIZ).

Results: HAZ remained fairly stable: mean changes from birth till 6 weeks, 26 weeks and 3-7 years were 0.07, 0.04 and 0.2 SD, respectively. BMIZ and WAZ showed considerable catch-up; 0.69 SD, 1.84 SD and 1.38 SD for BMIZ, and 0.25 SD, 0.89 SD and 0.60 SD for WAZ, respectively. 60-92% had at least one form of undernutrition and co-existence was frequent. Half the children remained stunted till 5 years, while underweight and wasting declined considerably from 0-6 months.

Conclusion: With appropriate counselling of parents, term low birth weight infants reared under adverse socioeconomic conditions show substantial catch-up growth in BMIZ and WAZ but not in HAZ. The long-term consequences of this excess weight over length gain need focused evaluation.

Keywords: *Catch-up growth, Poverty, Small for gestational age, Vitamin D.*

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Undernutrition is a major contributor to global disease burden in under-five children, especially in low- and middle-income countries (LMICs). The burden is estimated to be highest in South-central Asia [1]. India has a particularly high burden as per the latest national estimates; 35.5%, 32.1% and 19.3% are stunted, underweight and wasted, respectively [2]. Several determinants contribute to childhood under nutrition [1]. Small for gestational age (SGA) or low birth weight (LBW; birth weight <2500 g) are recognized as important predictors of undernutrition in LMICs [3,4]. Pooled data from 19 cohorts showed that term SGA children were at increased risk of being stunted (1.7 to 2.1 times), wasted (1.4 to 2.6 times) and underweight (1.7 to 2.4 times) between 12-60 months of age [4]. India has one of the highest burdens of LBW infants (21.4% in 2017) [5]. The majority (77-90%) of these LBW are full term but SGA [6-8]. It is, therefore, conceivable that a substantial proportion of under-five undernutrition in India is attributable to these undersized newborns.

Re-analysis of the WHO Multi-Centre Growth Reference Study indicated that children born to short mothers can achieve near normal postnatal growth, if reared in favorable conditions with adherence to internationally prescribed health and nutrition care recommendations [9]. Similarly, partial catch-up growth may be feasible with appropriate health and nutrition care under sub-optimal socioeconomic conditions, even in SGA or term LBW babies. The first six months are particularly important because of increased vulnerability of

rapid growth to nutritional and illness related insults and the potential for such anthropometric deficits to persist in childhood. A better understanding of this capability for catch-up growth and its facilitating factors will help optimize post-natal management in situations where women cannot be reached with appropriate interventions during pregnancy or where, even if they are reached, fail to benefit from the interventions.

A few studies on large LMICs cohorts of term LBW have evaluated the longitudinal growth and burden of under-nutrition [10], but not for all three anthropometric classifications. Further, there is limited data in urban poor on the incidence of and recovery from undernutrition and co-existence of its different forms, when health and nutrition care counselling approximate international recommendations. We report on these aspects from a prospective cohort of term LBW infants at periodic intervals from birth to 6 months of age and once later during childhood (2.8 to 6.8 years). We have previously analyzed the patterns of early growth in the same cohort and their influence on later anthropometry and bone density [11].

METHODS

The Delhi Infant Vitamin D Supplementation Study (DIVIDS-1) was a double blinded, randomized controlled trial of weekly vitamin D3 supplementation among term LBW Indian infants from birth to 6 months of age [12]. The trial was registered at ClinicalTrials.gov (NCT00415402). The primary outcome was infants' morbidity or mortality, whereas growth and vitamin D status at 6 months were secondary outcomes. We enrolled 2079 singleton term LBW (>37 weeks gestation; birth weight between 1800 and 2499 grams), aged less than 48 hours; and whose parents consented to parti-cipate and were living within 15 km radius of Safdarjung Hospital, New Delhi, between March, 2007 and July, 2010. Infants with any severe congenital abnormality, acute severe morbidity, or intention to move outside the study area before 6 months of age were excluded. At recruitment, anthropometry of the infant and socio-demographic profile of the family was recorded. Recruited infants were randomized either to receive weekly vitamin D3 supplements (1400 IU or 35 µg/week; n=1039) or identical looking and tasting placebo (n=1040) from first week till 6 months of age (maximum 25 doses) mixed in expressed breast milk. Anthropometric and clinical evaluation were performed at ages 6, 10, 14, 18, 22 and 26 weeks during scheduled visits to the hospital (n=1282) or at home for defaulters (n=207). During these visits, appropriate health care and nutrition counseling was done, primarily repeated advice on exclusive breastfeeding till 6 months age, complementary feeding, hygienic behavior, and age-appropriate immunizations. The parents were encouraged and facilitated to bring their infants to Safdarjung Hospital, whenever ill. Infants' anthropometry (in duplicate) was performed according to standard operating procedures [13]. Body weight was measured in minimal clothing, using an electronic weighing scale (sensitivity 0.01 kg). For measuring length, an infantometer was used (sensitivity 0.1 cm). A total of 1489 infants (Vitamin D group n=744; Placebo n=745) completed 6 months supplementation (**Fig. 1**).

We followed-up 912 participants from November, 2012 to January, 2014, between 2.8 and 6.8 years of age, during the DIVIDS-2 phase to investigate their anthropometry (in triplicate), bone and muscular strength, body composition and vitamin D status; these results are published elsewhere [11,14]. Weight was measured using digital scales (sensitivity 0.01 kg) and height using a wall mounted stadiometer (sensitivity 0.1 cm). Technical errors of measurements were within acceptable ranges [15].

Statistical analysis: Data were double entered in Microsoft Access and converted to SPSS ver. 20 for statistical analysis. Data integrity and distributions were checked and appropriate transformations were done. Age- and sex-specific internal *z* scores were computed for serial anthropometric measurements (length and weight) by LMS Chartmaker Light (Ver. 2.54, Medical Research Council, UK) [16]. Age intervals at various time points were defined as follows: 6 weeks: 27 to 57 days; 10 weeks: 58 to 85 days; 14 weeks: 86 to 113 days; 18 weeks: 114 to 141 days; 22 weeks: 142 to 169 days and 26 weeks: 170 to 232 days. Mixed modeling was used to explore the interaction of intervention effect with age and sex. As the intervention and age interaction term was significant (P<0.005), average estimated effect sizes were subtracted from internal *z* scores for treatment group of respective age interval. These adjusted *z* scores were back-transformed to compute weight and length. This adjustment was unnecessary for DIVIDS-2 because an intervention effect was not evident. WHO length (or height) for age (HAZ), weight for age (WAZ), BMI for age (BMIZ) and weight for length (or height) (WHZ) *z* scores were computed through SPSS user written program till 5 years of age [17]. Similarly, WHO *z* scores were computed for children above 5 years of age except for weight for height, for which no reference exists. We computed the prevalence of under-nutrition (HAZ or WAZ or WHZ<-2 SD) and severe undernutrition (HAZ or WAZ or WHZ<-3SD) at each time point. We determined the incidence of undernutrition (the proportion of children who were not stunted at an earlier time point but who were stunted later), as well as the incidence of recovery (the proportion of children who were stunted at an earlier time point but who were not stunted later). To estimate the likely bias in subjects' size due to loss to follow-up in a time interval, we adopted the approach detailed in **Web Appendix I**.

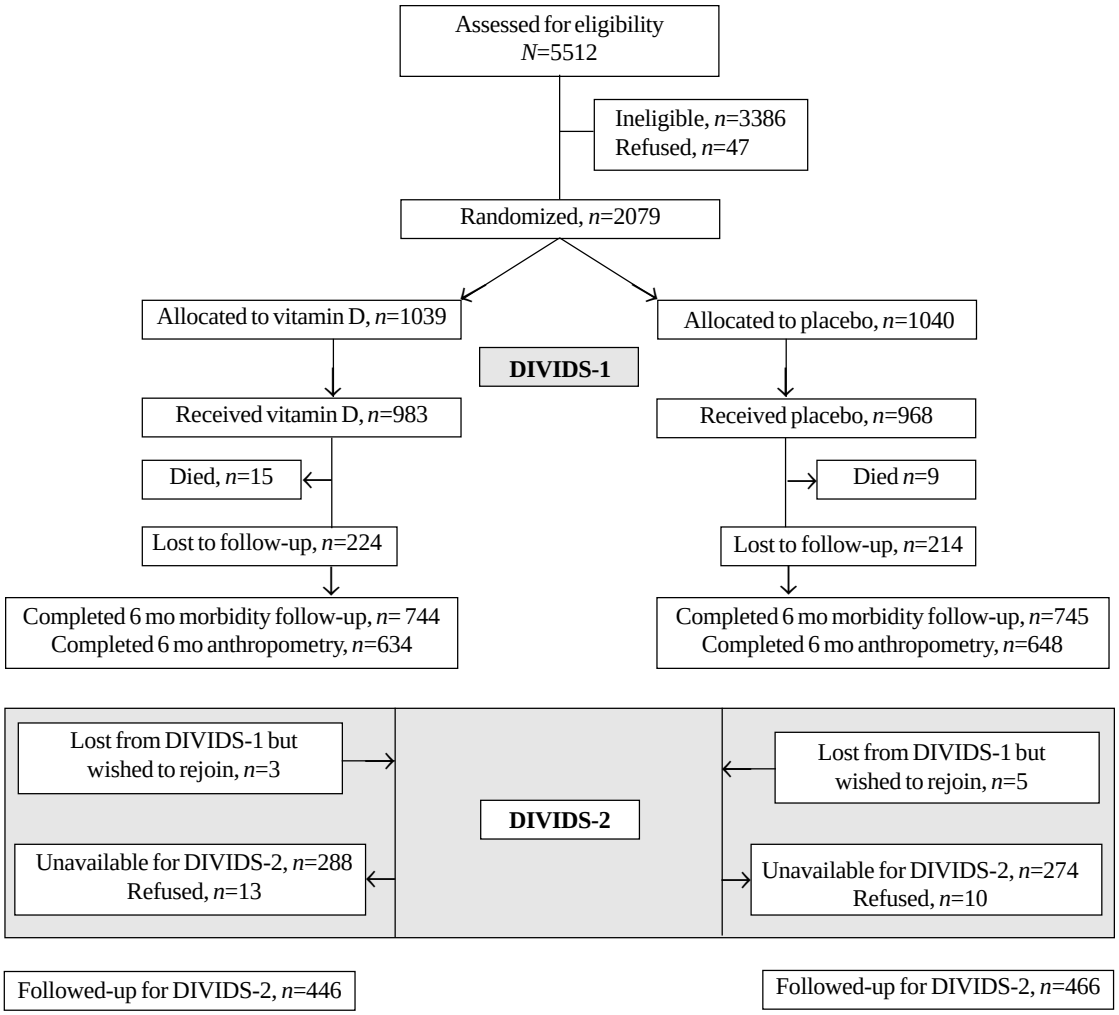

Fig. 1 Study flow chart of the original studies.

These studies were approved by the respective institutional ethics committees for both phases, and written informed consent was taken prior to recruitment.

RESULTS

Pertinent information on population characteristics detailed earlier [12] is summarized below. The mean (SD) maternal age at delivery was 23.5 (3.4) years. The population lived in urban poor settlements and had low education (51% fathers and 67% mothers only till middle school). The mothers were home-makers (97%) while fathers were employed (97%; only 1% as professionals). They were mostly residing in permanent dwellings (87%), in a joint or extended family system (55%), with substantial crowding (mean 6 family members per room). Only 39% had access to water supply through a private tap while just 13% households owned a flushed toilet. Participants not followed-up at the end of both phases were significantly more likely to be from poorer, smaller, and nuclear families and have less educated fathers and mothers [12,14]. These children also had significantly lower WHO *z* scores at earlier time points; 0.06-0.29 SD for HAZ, 0.01 to 0.3 SD for WAZ and 0.25 SD for BMIZ, at only 6 weeks of age.

The incidence rates (per child year) during the first six months of follow-up were: death 0.046 (95% CI 0.034 to 0.065) and any severe morbidity 0.44 (95% CI 0.39 to 0.49) [12]. Breastfeeding was almost universal; the median durations of exclusive and predominant breastfeeding were 15 and 20 weeks, respectively. At 26 weeks of age, exclusive breastfeeding was reported by 27% and predominant breast-feeding by 35% mothers. Predominant breastfeeding was defined [12] if breastmilk was the predominant source of nourishment; however, the infant may have received limited quantities of liquids (water and water-based drinks, fruit,

juice, oral rehydration solution), ritual fluids, and drops or syrups (vitamins, minerals, medicines). Nearly all (96%) infants were completely immunized for age as per the government recommended schedule.

Boys were significantly heavier and taller than girls (**Web Table I**). In general, WHO *z* scores were significantly different in boys till 26 weeks of age; 0.19 to 0.4 SD lower for HAZ, 0.1 to 0.36 SD lower for WAZ, and for WHZ 0.27 and 0.19 SD higher at 6 weeks and 10 weeks, respectively but 0.18 to 0.24 SD lower from 18 to 26 weeks.

Fig. 2 and **Web Table II** compare the observed and bias (due to loss to follow-up) corrected WHO anthropometric *z* scores for boys and girls combined. There was evidence of minimal bias; in the worst-case scenario, the observed values were higher by 0 to 0.08 SD only. Among the anthropometric indices, HAZ was the most stable; bias corrected mean change from birth till 6 weeks, 26 weeks and later childhood was 0.07, 0.04 and 0.2 SD, respectively. However, both BMIZ and WAZ showed considerable increase in *z* scores; the corresponding values were 0.69, 1.84 and 1.38 SD for BMIZ and 0.25, 0.89 and 0.60 SD for WAZ, respectively. For both these indices, the maximal catch-up had occurred at 26 weeks with some growth faltering thereafter (-0.46 SD for BMIZ and -0.29 SD for WAZ). Overall, BMIZ had a greater catch-up than WAZ (0.44 to 0.95 SD more). WHZ trajectory paralleled BMIZ but the catch-up was lower till 5 years (1.0 SD at 6 weeks, 0.25 SD at 26 weeks, and 0.19 SD later). The maximal transition in individual *z* scores for all anthropometric indices occurred between birth and 6 weeks in comparison to any two other successive time points later. Pearson correlation coefficients between birth and 6 weeks were 0.628 for HAZ, 0.463 for WAZ, 0.321 for BMIZ and 0.355 for WHZ ($P<0.001$ for all).

Fig. 3 depicts the overall and sex stratified prevalence of undernutrition (<-2 SD) for available participants. Stunting and underweight were more prevalent in boys while wasting was comparable in both sexes. The overall prevalence of stunting (~50%) remained unchanged from birth till 5 years. There was a progressive decline in prevalence of underweight (89% to 34%) and wasting (43% to 7%) from birth till 26 weeks; the decrease was most steep (~28%) from birth to 6 weeks. After this, the prevalence increased in later childhood; from 34% to 48% for underweight and 7% to 15% for wasting. Similar sex differences were evident for severe undernutrition (<-3 SD). Overall prevalence of severe stunting was relatively stable till 5 years (14-17%). Severe underweight progressively declined from 21% at 6 weeks to 8% at 26 weeks and increased to 12% in later childhood. Severe wasting (severe acute malnutrition) prevalence declined substantially from birth (9.4%) to 6 weeks (3.5%) and thereafter ranged between 2.3% and 0.8%.

Fig. 4 illustrates sequential incidence and recovery rates from undernutrition. Both rates were equivalent for stunting till 5 years while recovery was greater than incidence for wasting and underweight throughout except in later childhood for underweight. Viewed from another perspective (**Web Fig.1**), from 6 weeks till 26 weeks, roughly a quarter of children each were either never or always stunted while half were either stunted or normal at different time points. The corresponding proportions for underweight were one-third never, one-fifth always and half sometimes, and for wasted were three-fourths never, 1% always and one-quarter sometimes. For all three indices, in children not undernourished after 6 weeks, the maximal increase in mean *z* scores had occurred between birth and 6 weeks.

The potential combinations of undernutrition (stunting,

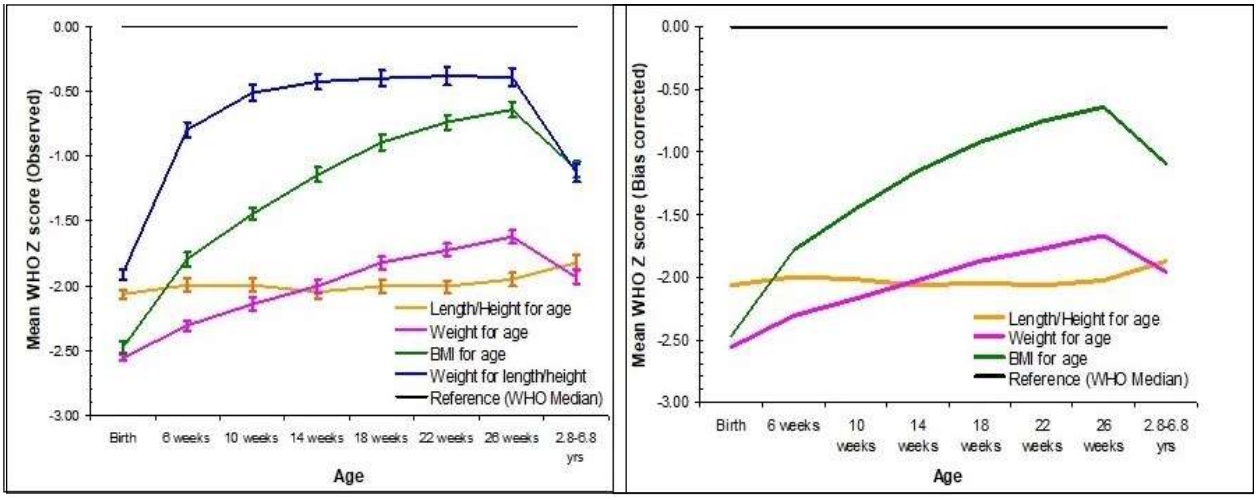

Fig. 2 Change over time in actual (left side) and bias corrected (right side) mean anthropometric WHO *z* scores for boys and girls combined for children born term low birth weight.

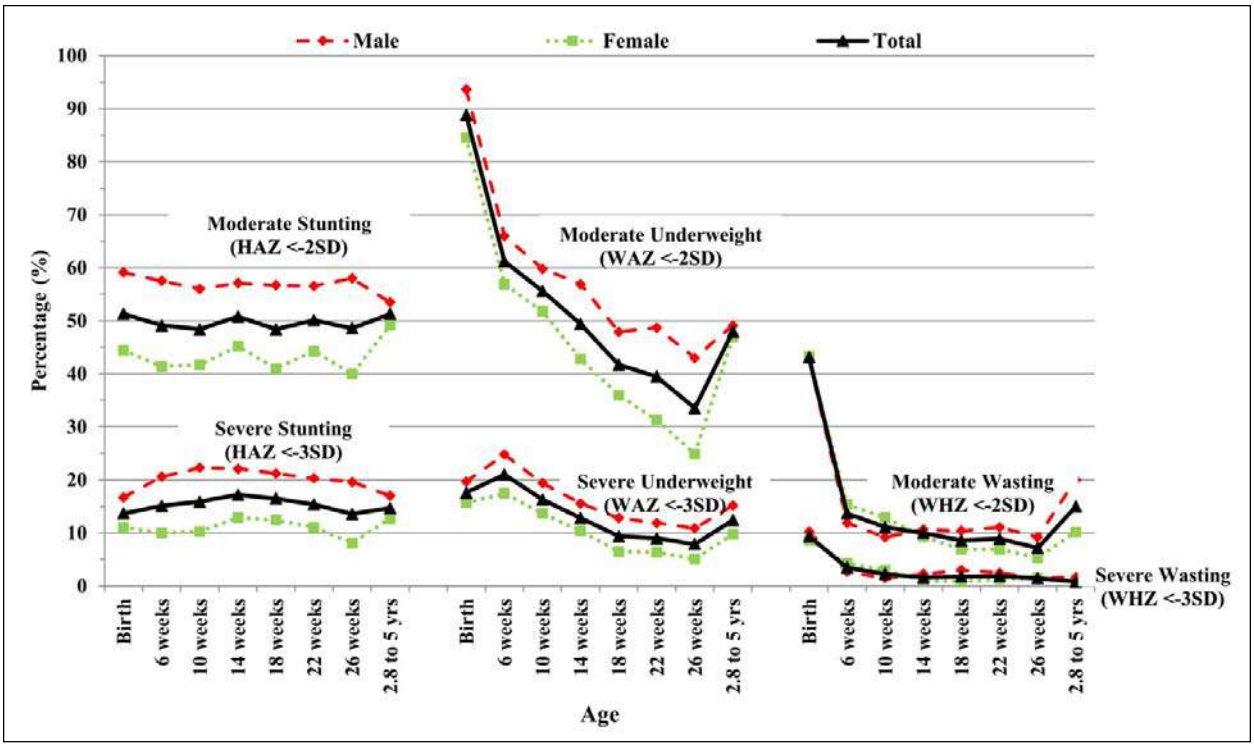

Fig. 3 Prevalence of stunting, underweight and wasting from birth till childhood among term low birth weight boys and girls.

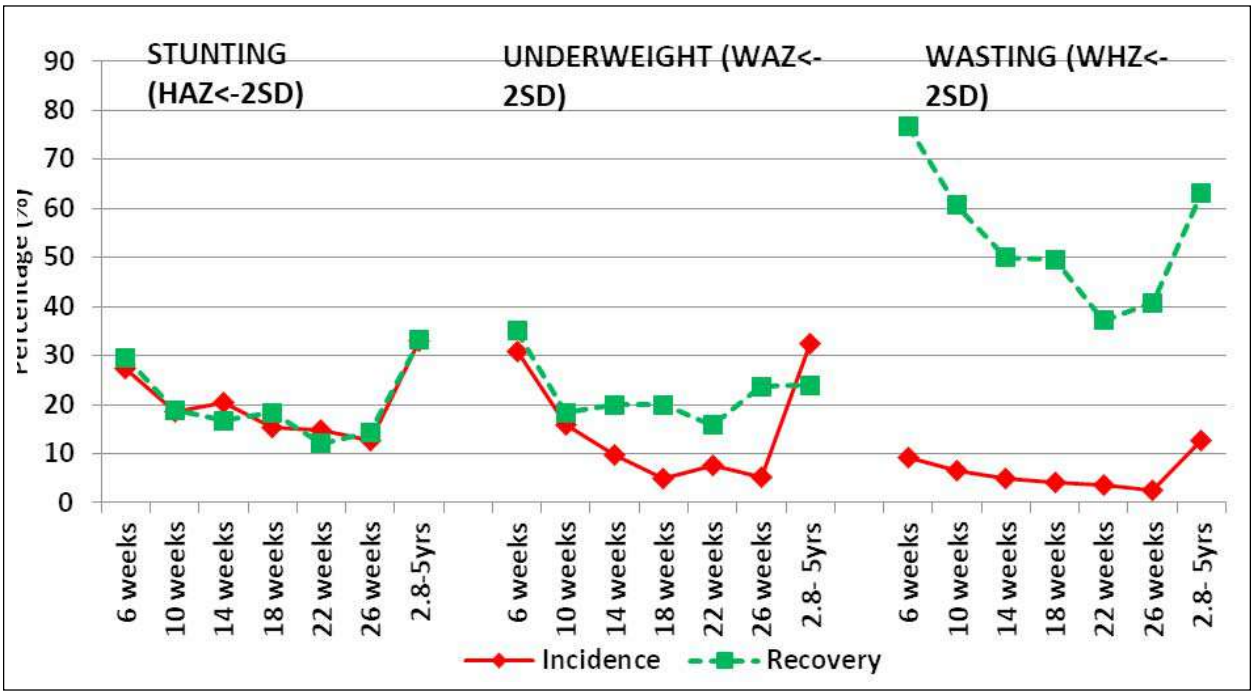

Fig. 4 Incidence of and recovery from stunting, underweight and wasting from 6 weeks till childhood in children born term low birth weight.

underweight and wasting) in an individual child are summarized in **Table I**. A vast majority had at least one form of undernutrition; the proportion declined from 92% at birth to 67% at 14 weeks and stabilized around 60% thereafter. Three-fourths had co-existence of any two forms of undernutrition at birth; the proportion pro-gressively declined to half at 6 weeks to a quarter at 26 weeks and again rose to 43% in later childhood. Stunting and underweight was the most common combination (24% to 49%), followed by underweight and wasting (41% at birth and 7% to 15% thereafter) whereas stunting and wasting was most infrequent (3% to 11%). Between 3% and 11% had all three forms of undernutrition.

DISCUSSION

Term LBW newborns reared in an unfavorable socio-economic milieu exhibited considerable improvement in weight for age, BMI for age and weight for height, and a slight increase in height for age until 5 years of age. Still, 60-92% had at least one form of anthro-pometric undernutrition and co-existence was frequent, with stunting and underweight being most common. Nearly half the children remained stunted till 5 years, while underweight and wasting declined considerably from 0-6 months.

These catch-up growth patterns are contradictory to analyses from demographic surveys in 54 LMICs, wherein substantial faltering was observed for WAZ and HAZ (0.75*z* and 1.5*z* at 24 months) and slight decline for WHZ (~0.25*z*) till 9 months age [18]. The differences relate to the cross-sectional nature of demographic surveys in which small for gestational age, appropriate for gestational age and large for gestational age participants are all included, thereby masking the heterogenous growth patterns. However, in conformity with the earlier reports [4,10], this study reaffirms that term LBW is an important predictor of undernutrition.

Studies from Europe and Americas have pre-dominantly focused on height, employing hetero-genous definitions of SGA and catch-up. Most term SGA births experienced catch-up growth to achieve a height >-2*z*; this was typically an early (~80% by 6 months) postnatal process, which was usually completed by 2 years [19-22]. In case-control reports based on 10-85 SGA children only, at 1-3 years, the average catch-up in WAZ and BMIZ was greater than LAZ [23-27]. The postulated reasons for the observed faster postnatal growth include regression to the mean, genetic factors [28], intrauterine restraint of fetal growth [29], and optimal health and nutrition care.

Paucity of comparable analyses from South Asia precludes robust external validation of disproportionately faster growth in weight and BMI in comparison to length, in similar adverse settings with appropriate counselling. A

Table I Undernutrition From Birth to Childhood in the Study Cohort

Age	*Any one*		*Any two*		*Stunted and wasted*		*Underweight and wasted*		*Stunted and underweight*		*Stunted, underweight and wasted*	
	N	*% (95% CI)*	*N*	*% (95% CI)*	*N*	*% (95% CI)*	*N*	*% (95% CI)*	*N*	*% (95% CI)*	*N*	*% (95% CI)*
Birth	2078	92.4 (91.2, 93.5)	2074	72.4 (70.4, 74.2)	1498[a]	8.7 (7.4, 10.2)	1498[a]	40.7 (38.1, 43.1)	2074	49.3 (47.1, 51.4)	1498[a]	8.7 (7.4,10.2)
6 wk	1674	71.1(68.9, 73.2)	1657	48.2 (45.7, 50.5)	1656	4.6 (3.6, 5.7)	1656	11.4 (9.9, 12.9)	1657	41.4 (39.0, 43.7)	1656	3.7 (2.9, 4.7)
10 wk	1609	67.9 (65.5, 70.1)	1590	44.2 (41.7, 46.6)	1590	2.8 (2.1, 3.7)	1590	9.5 (8.1, 11.0)	1590	37.5 (35.2, 39.9)	1590	2.8 (2.1, 3.7)
14 wk	1537	66.6 (64.2, 68.9)	1516	40.2 (37.8, 42.7)	1516	3.1 (2.3, 4.1)	1516	8.7 (7.3, 10.2)	1516	34.6 (32.2, 37.0)	1516	3.1 (2.3, 4.1)
18 wk	1440	61.2 (58.6, 63.6)	1421	34.5 (32.0, 36.9)	1421	2.7 (2.0, 3.7)	1421	7.6 (6.3, 9.1)	1421	29.6 (27.3, 32.0)	1421	2.7 (2.0, 3.7)
22 wk	1356	61.7 (59.1, 64.2)	1339	33.5 (30.9, 36.0)	1339	3.0 (2.2, 4.0)	1339	8.2 (6.8, 9.8)	1339	28.2 (25.8, 30.7)	1339	3.0 (2.2, 4.0)
26 wk	1270	57.5 (54.7, 60.1)	1253	28.4 (25.9, 30.9)	1253	3.0 (2.2, 4.1)	1253	7.0 (5.7, 8.5)	1253	24.4 (22.1, 26.8)	1253	3.0 (2.2, 4.1)
2.5-5 y	475	60.6 (56.1, 64.9)	474	42.6 (38.2, 47.1)	474	11.0(8.4, 14.1)	474	14.6 (11.6, 18.0)	474	39.0 (34.7, 43.4)	474	11.0 (8.4, 14.1)

N represents the numbers available and analyzed (denominator) for a particular age group with that specific undernutrition status and % indicates the percentage of children with that specific undernutrition status at that particular age group. [a]Birth length for 576 infants ranged between 40 -44.9 cm, which was below the lowest stated value in the publicly available WHO reference [17] for computing weight for length z score. Thus, their wasting status could not be determined.

WHAT IS ALREADY KNOWN?

- Term low birth weight (LBW) children contribute substantially to undernutrition burden in children below five years of age in India.
- There is limited data on longitudinal growth and undernutrition burden in term LBW from urban poor settings, with appropriate health and nutrition care counselling.

WHAT THIS STUDY ADDS?

- With appropriately counselled parents, term LBW infants reared under adverse socioeconomic conditions showed substantial catch-up growth in body mass index for age *z* scores and weight for age *z* scores, but not in height for age *z* scores.

recent study, conducted in two districts of Haryana, India reported only on linear growth trajectories till 6 months of age in a cohort of infants weighing 1500-2250 grams at birth of any gestational age [10]. The small for gestational age low birth weight (SGA-LBW) infants had lower average increase in HAZ in comparison to those who were appropriate for gestational (AGA-LBW; 0.88*z*). At 6 months of age, among the SGA-LBW, 55% showed catch-up growth, defined as an increase of HAZ >0.67*z*. The independent predictors of poor catch-up growth included poverty, home delivery, higher order birth (>4), male sex, term gestation, non-exclusive breastfeeding at 3 months, and past episodes of pneumonia. A tertiary care center in Delhi, in a follow-up of 34 term LBW (1500-2500 grams) at 7.2 months mean age, also documented a disproportionately greater increase in WAZ and WHZ in comparison to HAZ [30]. Similar findings were observed during the follow-up of 100 asymmetric SGA from upper strata in Chandigarh at 6 months, and at one-year. However, the increase in these indices was lower and comparable in symmetric SGA at 6 months, and at one-year [31]. The comparatively lower catch-up in length at 6 months age in our study could thus reflect poorer socioeconomic status, higher birth weight (1800-2500 grams), term gestation, and morbidity profile.

This cohort study from an urban poor setting in South Asia was conducted on a large sample size with a community follow-up, employing robust methodology and a strict quality control. It therefore provides confident programmatic expectations for subsequent growth and undernutrition burden among term LBW children living in adverse socioeconomic conditions while their parents received intense counselling on health and nutrition care for the first 6 months. The relatively lower mortality and serious morbidity rates, almost universal immunization, and good predominant or exclusive breastfeeding status till 6 months provide evidence of successful counseling and logistic support.

The following limitations merit consideration. First, after 6 months of age, there was no provision for logistic support, counseling (particularly for optimal complementary feeding) and periodic data collection on morbidity, immunization, and dietary intake. Nevertheless, the available growth data provide valuable insight into the residual effect of counseling in later childhood. Second, predictably there was substantial attrition with age in this setting (~38% at 6 months and ~56% later), predominantly due to outmigration. However, we adjusted for the small potential bias (0.0 to 0.08 SD) due to attrition on longitudinal growth. The undernutrition prevalence was slightly underestimated as it was based on available participants only.

A major public health implication of the study is that 60-70% of term LBW were noted to have at least one anthropometric deficit between 6 months to 5 years of age; thus, caregivers also need to consider low birth size as an important contributor to cross-sectionally detected undernutrition in under-five children. Disproportionately faster growth in weight or BMI has been linked with increased adiposity, liver fat, and adverse cardiometabolic biomarkers in childhood and later life [28,32,33]. Thus, there is a pressing need to create relevant and contextual evidence to inform public health guidelines for ensuring that intervention(s) to address anthropometric undernutrition do not inadvertently result in adverse cardiometabolic consequences in later life. Finally, the finding of maximal transition in individual *z* scores between birth and 6 weeks needs external validation and exploration, for example, to determine if it applies only to LBW infants who may catchup rapidly after being released from factors which constrained their growth in utero. If this early catch-up is seen widely, it could be a tool to aid clinical and public health decisions.

In conclusion, appropriately counselled, term LBW infants reared under adverse conditions show substantial catch-up growth in BMIZ and WAZ but not in HAZ. The long-term consequences of this excess weight over length gain should be evaluated through focused research.

Ethics clearance: The DIVIDS-1 study and the DIVIDS-2 study were approved by ethics committees of the participating

institutions. Authors declare that the study procedures conform to the principles laid down in the Declaration of Helsinki.

Contributors: The DIVIDS Cohort study was designed and initiated by GTK (Principal Investigator), HSS (Co-Investigator), and SF (Co-Investigator), and was supervised by GTK; HSS: conceptualized the research question in this manuscript; MK: was involved in data collection; SS: did the primary analyses and interpretation under the supervision of CO and HSS. MK, HSS: drafted the initial manuscript. All authors provided critical inputs into revision of the article and approved the finalized draft and are willing to be accountable for all aspects of the study.

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Competing interests: None stated.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I (a) Sex-specific Absolute Anthropometry from Birth till Childhood

	Boys		*Girls*		*P-value*
	No.	Mean (SD)	No.	Mean (SD)	
Weight (kg)					
Birth	972	2.23 (0.16)	1106	2.21 (0.17)	0.036
6 wk	794	3.61 (0.45)	879	3.43 (0.45)	<0.001
10 wk	752	4.45 (0.55)	857	4.17 (0.52)	<0.001
14 wk	724	5.13 (0.62)	811	4.77 (0.55)	<0.001
18 wk	682	5.68 (0.66	758	5.33 (0.59)	<0.001
22 wk	636	6.13 (0.71)	719	5.77 (0.65)	<0.001
26 wk	603	6.53 (0.73)	666	6.18 (0.70)	<0.001
2.8 - 6.8 y (total)	437	14.54 (2.76)	475	14.02 (2.40)	0.003
2.5 - 5 y (under 5)	230	12.95 (1.69)	245	12.72 (1.67)	0.134
5.1 - 6.8 y (above 5)	207	16.30 (2.64)	230	15.41 (2.28)	<0.001
Length/height (cm)					
Birth	970	45.78 (1.45	1104	45.47 (1.45	<0.001
6 wk	791	52.06 (1.93	867	51.58 (1.91	<0.001
10 wk	743	55.11 (2.15)	847	54.34 (2.02)	<0.001
14 wk	711	57.60 (2.26)	807	56.49 (2.15)	<0.001
18 wk	670	59.72 (2.29)	751	58.48 (2.10)	<0.001
22 wk	629	61.47 (2.21)	711	60.10 (2.10)	<0.001
26 wk	597	63.06 (2.19)	657	61.84 (2.03)	<0.001
2.8 - 6.8 y (total)	437	101.15 (8.44)	474	100.50 (7.94)	0.229
2.5 - 5 y (under 5)	230	95.12 (5.55)	244	95.05 (5.76)	0.893
5.1 - 6.8 y (above 5)	207	107.86 (5.52)	230	106.29 (5.45)	0.003

Web Table I (b) Sex-specific Anthropometric Length/height for age and weight for age WHO Z scores from Birth till Childhood

	Boys		*Girls*		*P-value*
	No.	Mean (SD)	No.	Mean (SD)	
Length/height for age z score (HAZ)					
Birth	970	-2.17 (0.77)	1104	-1.98 (0.78)	<0.001
6 wk	791	-2.18 (0.98)	867	-1.82 (0.95)	<0.001
10 wk	743	-2.19 (1.06)	847	-1.82 (0.97)	<0.001
14 wk	711	-2.23 (1.09)	807	-1.88 (1.00)	<0.001
18 wk	670	-2.19 (1.09)	751	-1.84 (0.96)	<0.001
22 wk	629	-2.18 (1.05)	711	-1.85 (0.95)	<0.001
26 wk	597	-2.16 (1.02)	657	-1.76 (0.90)	<0.001
2.8 - 6.8 y (total)	437	-1.84 (1.01)	474	-1.80 (0.95)	0.491
2.8 - 5 y(under 5)	230	-2.11 (0.99	244	-1.97 (0.94)	0.126
5.1 - 6.8 y (above 5)	207	-1.55 (0.95	230	-1.61 (0.93)	0.467
Weight for age z score (WAZ)					
Birth	972	-2.61 (0.43)	1106	-2.51 (0.47)	<0.001
6 wk	794	-2.26 (0.94)	879	-2.04 (0.94)	<0.001
10 wk	752	-2.26 (0.94)	857	-2.04 (0.94)	<0.001
14 wk	724	-2.12 (0.98)	811	-1.90 (0.90)	<0.001
18 wk	682	-2.00 (0.99)	758	-1.67 (0.90)	<0.001
22 wk	636	-1.90 (1.00)	719	-1.57 (0.93)	<0.001
26 wk	603	-1.81 (1.00)	666	-1.45 (0.95)	<0.001
2.8 - 6.8 y (total)	437	-1.91 (1.00)	475	-1.94 (0.91)	0.639
2.8 - 5 y (under 5)	230	-2.00 (0.93)	245	-1.94 (0.85)	0.465
5.1 - 6.8 y (above 5)	207	-1.82 (1.06)	230	-1.95 (0.98)	0.189

Web Table I (c) Sex-specific Weight for length/height and BMI-for-age WHO Z scores from Birth till Childhood

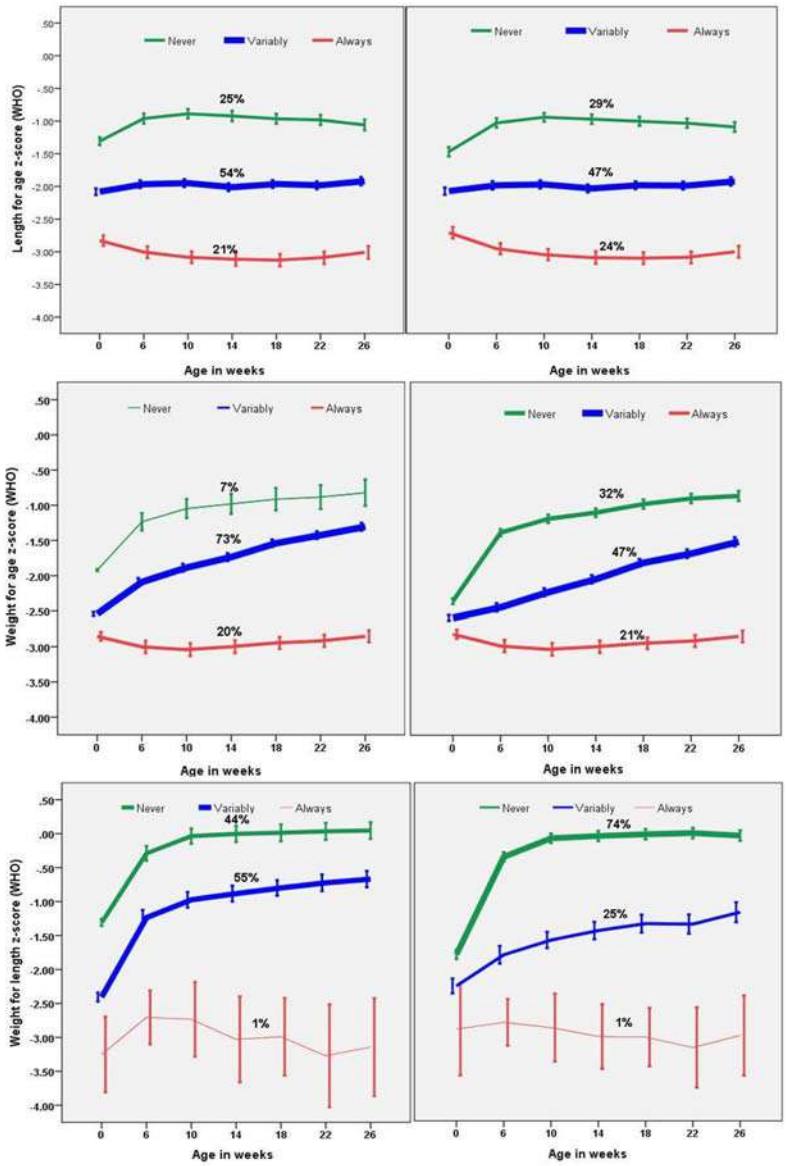
	Boys		*Girls*		*P-value*
	No.	Mean (SD)	No.	Mean (SD)	
Weight for length/height Z-score (WLZ)					
Birth*	738	-1.90 (0.82)	760	-1.91 (0.79)	0.800
6 wk	790	-0.66 (1.14)	866	-0.93 (1.19)	<0.001
10 wk	743	-0.41 (1.19)	847	-0.60 (1.20)	0.001
14 wk	711	-0.42 (1.31)	805	-0.43 (1.18)	0.880
18 wk	670	-0.49 (1.29)	751	-0.31 (1.20)	0.005
22 wk	628	-0.51 (1.29)	711	-0.27 (1.19)	<0.001
26 wk	596	-0.49 (1.23)	657	-0.30 (1.12)	0.005
2.8 - 5 y	230	-1.17 (0.90)	244	-1.09 (0.76)	0.311
BMI-for-age Z-score (BMIZ)					
Birth	970	-2.54 (0.71)	1104	-2.42 (0.73)	<0.001
6 wk	791	-1.86 (1.02)	866	-1.74 (1.02)	0.012
10 wk	743	-1.50 (1.06)	847	-1.40 (1.04)	0.067
14 wk	711	-1.19 (1.16)	805	-1.10 (1.03)	0.130
18 wk	670	-0.99 (1.18)	751	-0.80 (1.09)	0.002
22 wk	628	-0.85 (1.23)	711	-0.65 (1.13)	0.002
26 wk	596	-0.72 (1.20)	657	-0.57 (1.11)	0.017
2.8 - 6.8 y (total)	437	-1.07 (0.99)	474	-1.13 (0.85)	0.287
2.8 - 5 y (under 5)	230	-0.91 (0.86)	244	-0.96 (0.74)	0.510
5.1 - 6.8 y (above 5)	207	-1.24 (1.10)	230	-1.31 (0.92)	0.439

** Birth length for 576 infants ranged between 40 - 44.9 cm, which was below the lowest stated value in the publicly available WHO reference [17] for computing weight-for-length Z-score. Thus, their wasting status could not be determined.*

Web Table II Comparison of Actual and Bias Corrected Means Due to Loss to Follow-up for WHO Anthropometric *z* scores at Different Time Points

Age	*Actual*		*Bias corrected Mean*			
	N	*Mean*	*N*	*Plan A*[*]	*Plan B*[▽]	*Plan C*[#]
Height for age z score						
Birth	2074	-2.07	2074	-2.07	-2.07	-2.07
6 wk	1655	-1.99	2074	-2.00	-2.00	-2.00
10 wk	1587	-1.99	2074	-2.01	-2.01	-2.02
14 wk	1514	-2.04	2074	-2.05	-2.05	-2.07
18 wk	1416	-2.00	2074	-2.03	-2.03	-2.05
22 wk	1336	-2.01	2074	-2.03	-2.03	-2.07
26 wk	1251	-1.95	2074	-1.98	-1.98	-2.03
2.8-6.8 yrs (mean age 5 yrs)	910	-1.82	2074	-1.83	-1.83	-1.87
Weight for age z score						
Birth	2078	-2.56	2078	-2.56	-2.56	-2.56
6 wk	1672	-2.31	2078	-2.31	-2.31	-2.31
10 wk	1608	-2.14	2078	-2.15	-2.17	-2.17
14 wk	1534	-2.00	2078	-2.01	-2.01	-2.03
18 wk	1439	-1.82	2078	-1.83	-1.85	-1.87
22 wk	1355	-1.72	2078	-1.73	-1.75	-1.78
26 wk	1269	-1.62	2078	-1.62	-1.63	-1.67
2.8-6.8 yrs (mean age 5 yrs)	911	-1.93	2078	-1.94	-1.93	-1.96
BMI for age z score						
Birth	2074	-2.48	2074	-2.48	-2.48	-2.48
6 wk	1654	-1.80	2074	-1.79	-1.79	-1.79
10 wk	1587	-1.44	2074	-1.44	-1.46	-1.46
14 wk	1512	-1.14	2074	-1.14	-1.15	-1.16
18 wk	1416	-0.89	2074	-0.89	-0.90	-0.92
22 wk	1335	-0.74	2074	-0.74	-0.75	-0.76
26 wk	1250	-0.64	2074	-0.63	-0.62	-0.64
2.8-6.8 yrs (mean age 5 yrs)	910	-1.10	2074	-1.10	-1.10	-1.10

Overall bias was estimated using correlation coefficient and mean standardized Z-scores for Plans A, B and C. Mean standardized Z-scores were interpolated for loss to follow up using measurements at birth for ***[*]Plan A,*** *immediately preceding time point for* ***[▽]Plan B*** *and nearest earlier time points at which they were available for* ***[#]Plan C****. Back transformation was done to express them into actual units. Bias corrected mean was computed by weighted pooling of subjects, those who were available and those with interpolated values. The difference between actual and bias corrected mean (among all plans) ranged between 0.00 and 0.08 SD.*



Panel A represents undernutrition assessment including birth; Panel B represents undernutrition assessment excluding birth. Error bars represents 95% CI. Sample sizes for Panel A for length for age was 877, weight for age was 934 and weight for length was 647. The corresponding sample sizes for Panel B were 878, 934, and 874, respectively.

Web Fig. 1 Longitudinal Tracking of Undernutrition Till 6 of Age for Children With Anthropometric Measurements available at all Time Points

Web Appendix 1. Statistical methods for estimating bias corrected anthropometry

We considered all subjects with size known at the beginning of an interval and divided them according to whether their size was known at the end of the interval. We standardized the size measurements for those available at both time points to have mean zero and standard deviation unity at each time point, and calculated the correlation between them. We used the standardizing transformation at the beginning of interval to express the mean initial size for those lost to follow-up as a SD score. We multiplied this by the correlation coefficient to estimate the mean standardized score at the end of the interval for these subjects. To express this in units of measurement we back-transformed using the standardizing transformation at the end of the interval. In a further model we used the shortest intervals available to estimate bias. For example, in estimating the bias for subjects with unknown size at age 18 weeks we divided them into four subsets: those with known size at 14 weeks; those with known size at 10 weeks, but not at 14 weeks; those with known size at 6 weeks, but not at 10 or 14 weeks; those with known size at birth, but not at 6, 10 or 14 weeks. We used the procedure defined above to estimate the bias in each of these subsets. For robustness, we used the correlation coefficient for size at the beginning and end of an interval computed from all available pairs. Thus, in the bias assessment for the subset using birth and 18 weeks, we used the correlation of size at these ages for all subjects, regardless of whether there were intermediate measurements of size at 6, 10 and 14 weeks. We then pooled these results to get an estimate of bias corrected means.

RESEARCH PAPER

Socio-cultural Adaptation and Validation of Ages and Stages Questionnaire (ASQ 3) in Indian Children Aged 2 to 24 Months

SHEFFALI GULATI,[1] ANIL ISRANI,[1] JANE SQUIRES,[2] AJAY SINGH,[3] PRIYANKA MADAAN,[1] GAUTAM KAMILA,[1] RM PANDEY[4]

[1]*Center of Excellence and Advanced Research on Childhood Neuro-developmental Disorders, Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.*

[2]*Center on Human Development College of Education, University of Oregon, Oregon, US.*

[3]*College of Education, Texas A & M International University, Texas, US.*

[4]*Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India.*

Correspondence to: Prof Sheffali Gulati, Professor and Chief, Center of Excellence and Advanced Research on Childhood Neuro-developmental Disorders, Child Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India. sheffaligulati@gmail.com

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Objective: To socio-culturally adapt and validate a Hindi language version of Ages and Stages Qustionnaire (ASQ-3) in Indian children aged 2-24 months.

Methods: This cross-sectional study was conducted at a tertiary-care center between March, 2017 and April, 2019, children "at-risk" for developmental delay of either gender aged 2-24 months. Socio-cultural adaptation was done through interaction among 37 subject experts followed by validation. After piloting in 20 children, modified ASQ-3 was validated in 568 at-risk children (4 age-groups: 2-7, 7-13, 13-19 and 19-24 months). Validation was done against Development Assessment Scale for Indian Infants (DASII).

Results: After screening 654 children, 568 were enrolled. Among these, 420 had developmental delay on DASII while 18 failed to be identified on ASQ-3 (4.3%). Overall sensitivity and specificity of Hindi language Indian-adaptation of ASQ-3 in detecting developmental delay were 95.9% (95%CI: 93.6%-97.5%) and 81.7% (95%CI: 74%-87.9%), respectively with a positive predictive value (PPV) of 94.6% (95%CI: 92%-96.5%) and negative predictive value (NPV) of 85.6% (95%CI: 78.2%-92.2%). The sensitivity and specificity for motor delay were 96.1% (93.8%-97.7%) and 92.4% (86.4%-96.3%) [PPV: 97.7% (95.8%-98.9%); NPV: 87.7% (81%-92.7%)]. Sensitivity and specificity for mental delay were 95.5% (93.1%-97.2%) and 95.3% (90.1%-98.3%) [PPV: 98.6% (97%-99.5%); NPV: 85.9% (79.1%-91.2%)].

Conclusion*:* The Hindi language Indian-adaptation of ASQ-3 had good psychometric properties with high sensitivity for developmental delay (95.9%), mental delay (95.5%), and motor delay (96.1%), suggesting it to be a good screening tool for neurodevelopmental delay.

Keywords*: Development assessment, Developmental screenin*g, *Hindi, Neurodevelopmental disorders*.

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Developmental screening is a widely followed strategy for identifying children at risk who need further monitoring and assessment [1-3]. In low- and middle-income countries (LMICs) like India where routine developmental screening is not an office practice, late referral is common for children with developmental delays and disabilities [4]. The prevalence of global developmental delay in Indian infants (under 2 years) varies with region and the tool used for screening, and ranges between 1% - 2.5% [5].

Developmental screening is difficult to adapt in India due to a huge burden of developmental delays, expense involved, lack of an acceptable tool for nationwide use, time constraints, and lack of skilled personnel. Several screening tools have been developed to facilitate screening in different contexts and countries. However, many of them are time-consuming, complicated, and require certain specific instruments and trained personnel to interpret. Also, parents are often not involved in these tests. Hence, a parent-administered questionnaire may be more practical, resulting in improved follow-up rates. Ages and Stages Questionnaires (ASQ) are parent-completed questionnaires, which have been adapted cross-culturally and validated in multiple countries [6]. ASQ is being considered as a promising global screening tool [7]. This has been translated into 16 languages and has been used or studied in around 23 LMICs [7,8].

The Third edition of ASQ (ASQ-3) was completed in 2008. A previous study assessed the feasibility of third edition of ASQ (ASQ-3) "home procedure" in a field trial in nutritional research [9]. However, to the best of our knowledge, ASQ-3 has not been validated for developmental screening in India. Hence, the current study was envisaged to develop an Indian adaptation of ASQ-3 and determine its diagnostic utility in Indian infants and children compared with an established gold standard reference test, the Developmental Assessment Scale for Indian Infants (DASII).

METHODS

This cross-sectional study was performed at a tertiary-care center in Northern India over two years (March, 2017-April, 2019) after approval from the institutional ethics committee.

At risk children (as defined by National Neonatology Forum practice guidelines) [10] of either gender aged 2 to 24 months were enrolled from the out-patient services of department of pediatrics after informed consent from the parents or legally accredited representatives. Risk factors included birth weight <2500 g or preterm gestation, small for date (<3rd centile) at birth, neonatal sepsis, hypoglycemia and/or symptomatic polycythemia, central nervous system infections, mechanical ventilation>24 hours, hypotension requiring inotropic support, intraventricular hemorrhage, hypoxic ischaemic encephalopathy, neonatal jaundice with encephalopathy or requiring exchange transfusion, twins or multiple pregnancy, major malformation, infants of HIV positive mothers, genetic or chromosomal anomaly, inborn errors of metabolism, epilepsy, and suboptimal home environment (poor socioeconomic and coping status of parents) [10]. Children not accompanied by primary caregiver, those with poor general condition (Breathing difficulty, hemodynamic instability, or altered sensorium), and refusal of consent were excluded. Children were included in 4 age groups: 2-7 months, 7-13 months, 13-19 months, and 19-24 months. In each of the above-mentioned four groups, children continued to be enrolled till 100 subjects were diagnosed with developmental delay according to the reference standard DASII.

The ASQ-3 (21 age-based questionnaires with 30 items each) assesses development in five domains: gross motor, fine motor, communication, problem solving and personal social [11]. Every item is scored as 10, 5, or 0 based on the response: Yes,' 'Sometimes,' or 'Not yet,' respectively. Domain scores are obtained by the sum of the items. Children with ASQ score below the cutoff (< –2SD) in any of the domain are taken as screen positive and with those between 1 to 2 SD below mean are considered in monitoring zone [11]. For the present study, 13 age-based questionnaires were used (2 months, 4 months, 6 months, 8 months, 9 months, 10 months, 12 months, 14 months, 16 months, 18 months, 20 months, 22 months, and 24 months).

The study group had previously evaluated psychometric properties of Hindi translation of ASQ-3 in 196 "at risk" infants and children aged 1 month to 2 years as compared with a gold standard reference test (DASII). The psychometric properties showed a relatively lower sensitivity in the mild risk factor group. Hence, the current study involving evaluation of a socio-culturally adapted version was undertaken.

Inputs for socio-cultural adaption were incorporated in the questionnaire following multiple interactions with subject experts (37 members across India were approached) through emails, teleconferences, and meetings. Translation to Hindi and back-translation was done by two independent experts. The Indian-adapted versions of ASQ (in English and Hindi) were finalized. These Indian-adapted versions were piloted in 20 children [12 boys; aged 2-24 months (5 each in age group 2-7 months, 7-13 months, 13-19 months, 19-24 months)]. Of these 20 children, 11 had motor delay and 13 had delay in mental domain on DASII (gold standard) [12]. Overall, 12 children (60%) had developmental delay (Developmental quotient (DQ)<70) on DASII. In the pilot study, Indian-adapted version of ASQ-3 was found to have 89% sensitivity and 92% specificity for diagnosing developmental delay in children aged 2-24 months. After successfully establishing the feasibility and ruling out any gross disparity in psychometric efficacy of both these tests, the questionnaire was accepted for the study without any other modification.

Developmental Assessment Scale for Indian Infants (DASII) is considered as gold standard for developmental assessment in Indian infants [12]. It is applicable from birth to 30 months of age and provides motor developmental quotient (DQ), mental DQ, and composite DQ. The normative values on DASII have been obtained based on a sample of Indian Children [12]. For the purpose of current study, developmental delay was defined as DQ score ≤70 (≤-2SD) on DASII in either the mental or motor scale. Since ASQ is a screening tool, screen positivity on ASQ was also validated against DASII cutoffs of ≤77.5 (≤-1.5SD) and ≤85 (≤-1SD).

The at-risk children in each age subgroup underwent developmental evaluation using DASII and ASQ. The personnel administering both the tests were different and blinded to the outcome of the other test in each child. By random sequence generation, half of the subjects underwent DASII evaluation first and the other half, ASQ first. After evaluation, reports/assessment was sealed and sent to the study coordinator the same day. In a particular age group, patient enrolment was stopped only when 100 patients diagnosed with developmental delay using DASII were enrolled.

Statistical analysis: Data were recorded in a Microsoft Excel spreadsheet (Microsoft Corp.) and analyzed using SPSS. Categorical variables were compared using Chi square or Fischer exact test. Depending upon the distribution of continuous variables, Student t test was used for parametric variables, and Mann Whitney U test was used for non-parametric variables. Differences with *P* value of 0.05 or lower was considered significant. Pearsons correlation

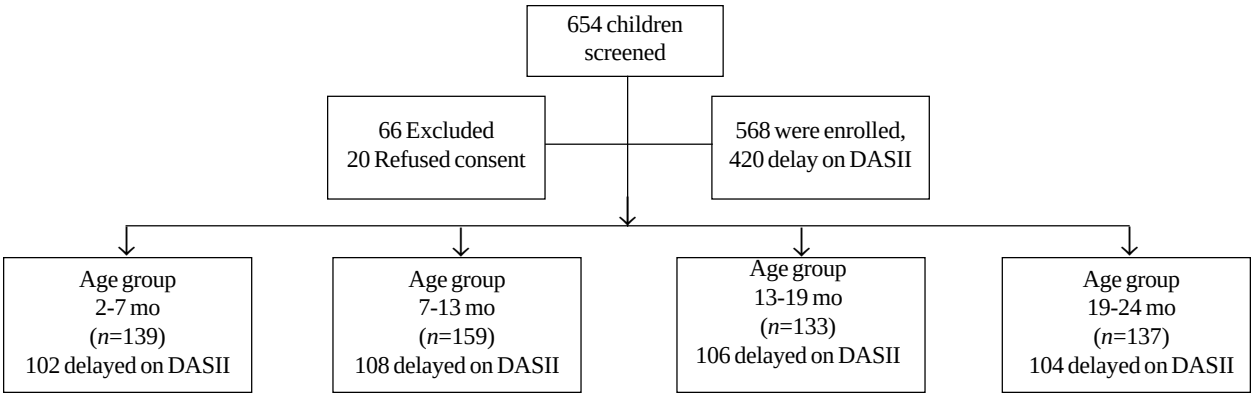

Fig. 1 Participant enrollment in various age subgroups.

coefficient was used for studying the correlation of various variables.

RESULTS

After finalization of the tool, 654 children were screened for inclusion in the study. Of these, 568 children (66% boys) were finally enrolled (**Fig. 1**). The median age was 13 months (IQR: 8,19 months) (66% boys) (**Table I**).

Significant delay on DASII was seen in 420 enrolled children. Among these, ASQ failed to identify developmental delay in 18 (4.3%) children. Corresponding figures in the various age groups were: 2-7 months, 5 (4.9%); 7-13 months, 7 (6.5%); 13-19 months, 3 (2.8%); and 19-24 months, 3 (2.9%).

The overall sensitivity and specificity of Indian adaptation of ASQ3 in detecting developmental delay were 95.9% (95% CI: 93.6%-97.5%) and 81.7% (95% CI: 74%-87.9%) with a positive predictive value (PPV) of 94.6 % (92%-96.5%) and negative predictive value (NPV) of 85.6% (78.2%-92.2%). The sensitivity and specificity of Indian adaptation of ASQ-3 for motor delay were 96.1% (93.8%-97.7%) and 92.4% (86.4%-96.3%); and for mental delay (communication, personal social and problem solving) were 95.5% (93.1-97.2%) and 95.3% (90.1%-98.3%). (**Table II**). A correlation between ASQ and DASII was observed for mental delay (r=0.87, P<0.001) as well as for motor delay (r=0.72, P <0.001). Additional analysis was done for higher DQ cutoff <85 and 77.5 (**Web Table I** and **II**).

DISCUSSION

We presented the psychometric properties of Indian-adapted version of ASQ-3, highlighting its potential as a good developmental screening tool. Considering the American Academy of Pediatrics standards for high-quality developmental screening tests (sensitivity and specificity of 70-80%), ASQ-3 is a high-quality developmental screening tool [3]. The psychometric properties of Indian-adapted Hindi language version were comparable to those in ASQ-3 technical report on a sample of 579 children [11,16]. As per the technical report, the sensitivity and specificity of ASQ-3 in the age group of 2- 24 months are 87.6% and 83.2%, respectively [16]. The sensitivity in the current study ranged from 82.8% to 95.9% depending on DQ cutoff on DASII used for validation. Like ASQ-2 and DASII, ASQ-3 and DASII have good correlation for domain scores (for DQ cutoff< 70) [8].

ASQ-3 questionnaires are commercially available in multiple languages [7]. Subsequently, these have been translated, cross-culturally adapted, and validated in multiple

Table I Baseline Characteristics of the Participants in the Study (*N*=568)

Characteristics	*Value*
Age (mo)[a]	13 (8,19)
Age groups	
2-7 mo	139 (25)
7-13 mo	159 (28)
13-19 mo	133 (23)
19-24 mo	137 (24)
Male gender	375 (66)
Cesarean delivery	72 (12.7)
Risk status[b]	
Low risk	55 (9.9)
Moderate risk	251 (44.2)
High risk	262 (46.1)
Primary caregiver respondent	
Mother	496 (87.3)
Father	49 (8.6)
Others	23 (4.0)

Values in no. (%) or [a]median (IQR). [b]Risk stratification as per National Neonatology Forum [10].

Table II Psychometric Properties of Ages and Stages Questionnaire (ASQ) 3 Against Developmental Assessment Scale for Indian Infants (DASII) as Gold Standard (*N*=568)

Psychometric properties	*Developmental delay, n=420*	*Mental delay, n=420*	*Motor delay, n=420*
Sensitivity (95% CI)	95.9 (93.6-97.5)	95.5 (93.1-97.2)	96.1 (93.8-97.7)
Specificity (95%CI)	81.7 (74 -87.9)	95.3 (90.1-98.3)	92.4 (86.4-96.3)
Positive predictive value (95%CI)	94.6 (92-96.5)	98.6 (97-99.5)	97.7 (95.8-98.9)
Negative predictive value (95%CI)	85.6 (78.2-92.2)	85.9 (79.1-91.2)	87.7 (81-92.7)
Positive likelihood ratio (95%CI)	5.23 (3.6-7.5)	20.4 (9.3-44.5)	12.6 (6.9-2.3)
Negative likelihood ratio (95%CI)	0.050 (0.03-0.08)	0.047 (0.03-0.1)	0.0421 (0.03-0.1)

Developmental delay on DASII as DQ score ≤70 (≤ -2SD).

countries with acceptable psychometric properties [7,17-26]. Therefore, ASQ is often considered as a global screening scale as it is brief, time-efficient, and cost-effective tool [6]. With huge birth cohorts each year, parent-based questionnaires for developmental screening in India are the need of the hour. Also, the pandemic related restrictions in the last two years have possibly increased the burden of undiagnosed and untreated delays and different strategies (such as general movement assessment) are being proposed for neurodevelopmental follow up of at-risk babies [27-29]. In these testing times, ASQ is likely to gel well with tele-child neurology [31]. The community validation study of Trivandrum Development Screening Tool (TDSC) observed a sensitivity and specificity of 84.6% and 90.8%, respectively with a negative predictive value of 99.23% [32]. Another useful tool, Baroda Development Screening Tool (BDST), based on the Bayley Scales of Infant Development (BSID) has a sensitivity and specificity ranging between 65-95% [33]. Compared to these existing screening tools used for developmental assessment, the Indian adaptation of ASQ has a better sensitivity and specificity than the BDST, while the values are similar to those observed with the TDSC. However, the main advantage of the Indian adaptation of the ASQ is that only 12-18 min are required for the development assessment, which may make it easier to use in busy out patient settings.

To the best of our knowledge, this is the first study validating ASQ-3 (which is a widely accepted screening tool) for developmental screening in a large cohort of Indian children. However, the validation of ASQ was done in at risk children (ranging from low to high risk). Also, this was a hospital-based study with a possible referral bias and most of the enrolled children were at moderate to high risk for developmental delay. Moreover, India is a multilinguistic country, but this translation was done only in the Hindi language.

The Indian adaptation of Ages and Stages Questionnaire has good psychometric properties for at risk children aged 2-24 months. Further studies validating translations into different regional languages with large community-based samples are needed.

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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Psychometric Properties of Ages and Stages Questionnaire (ASQ) in Comparison With Developmental Assessment Scale for Indian Infants (DASII) as Gold Standard (*N*=568)

Psychometric properties	*Developmental delay (n=427)*	*Mental delay (n=415)*	*Motor delay (n=404)*
Sensitivity (95%CI)	88.2% (85-91)	90.2% (87.1-92.8)	91% (87.9-93.5)
Specificity (95%CI)	95.2% (88.3-98.7)	89.8% (82.5-94.8)	79% (70.8-85.8)
Positive predictive value (95%CI)	99.1% (97.6-99.7)	97.4% (95.4-98.7)	94% (91.3-96)
Negative predictive value (95%CI)	58.4% (49.7-66.7)	68.3% (60-75.9)	71% (62.7-78.4)
Positive likelihood ratio (95%CI)	18.5% (7.12-48.2)	8.86% (5.06-15.5)	4.34 (3.08-6.11)
Negative likelihood ratio (95%CI)	0.124% (0.096-0.159)	0.106% (0.082-0.145)	0.114 (0.837-0.155)

Developmental delay on DASII as DQ score ≤77.5 (≤-1.5SD).

Web Table II Psychometric Properties of Ages and Stages Questionnaire (ASQ) in Comparison With Developmental Assessment Scale for Indian Infants (DASII) as Gold Standard

Psychometric properties	*Developmental delay (n=429)*	*Mental delay (n=422)*	*Motor delay (n=422)*
Sensitivity (95% CI)	82.8 (79.3-86)	84.4 (80.9-87.5)	85.3 (81.8-88.3)
Specificity (95% CI)	96 (86.3-99.5)	94.1 (85.6-98.4)	89% (79.5-95.1)
Positive predictive value (95% CI)	99.5% (98.3-99.9)	99.1% (97.6-99.7)	98.1 % (96.4-99.2)
Negative predictive value (95% CI)	35% (27.1-43.6)	45.1% (36.7-53.6)	47.1 % (38.6-55.8)
Positive likelihood ratio (95% CI)	20.7 (5.32-80.5)	14.3 (5.54-37.2)	7.78 (4.04-15)
Negative likelihood ratio (95% CI)	0.179 (0.147-0.218)	0.166 (0.134-.205)	0.166 (0.132-.208)

Developmental delay on DASII as DQ score ≤85 (≤-1SD).

RESEARCH PAPER

Therapeutic Response to Sublingual Methylcobalamin in Children With Vitamin B12 Deficiency Anemia

CHAHAT SAXENA,[1] SWETA KUMARI,[1] POOJA DEWAN,[1] SUNIL GOMBER,[1] RACHNA AGARWAL,[2] SANGEETA SHARMA,[3] NITA RADHAKRISHNAN,[4] MANIDEEPA MAJI[4]

[1]*Department of Pediatrics, University College of Medical Sciences & GTB Hospital, Delhi.*
[2]*Department of Neurochemistry, Institute of Human Behaviour and Allied Sciences, Delhi.*
[3]*Department of Neuropsychopharmacology, Institute of Human Behaviour and Allied Sciences, Delhi.*
[4]*Department of Pediatric Hematology Oncology, Post Graduate Institute of Child Health, Noida, Uttar Pradesh.*

Correspondence to:
Dr Pooja Dewan,
Professor of Pediatrics,
University College of Medical Sciences, Delhi.
poojadewan@hotmail.com
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Objective: To evaluate the efficacy and safety of sublingual methylcobalamin for the treatment of vitamin B12 deficiency anemia in children. **Methods:** A **s**ingle arm intervention study was conducted between November, 2020 and April, 2022 in children aged 1-12 years with vitamin B12 deficiency anemia. Children aged 1-6 years received a tablet of methylcobalamin (1500 mcg) by sublingual route every alternate day (three doses) while those aged 7-12 years received five such doses. Thereafter, one such sublingual tablet was given weekly and all participants were followed-up for 6 weeks. **Results:** 37 children with a mean (SD) age of 8.2 (4.1) years were treated and followed-up. On day 10, no child needed rescue therapy with parenteral methylcobalamin. After 6 weeks, the mean (SD) serum cobalamin increased from 123.3 (35.5) pg/mL to 507.3 (274.2) pg/mL (P<0.001), plasma homocysteine decreased from 48.9 (17.8) µmol/L to 16.3 (8.5) µmol/L (P<0.001), the mean (SD) hemoglobin increased by 2.3 (1.1) g/dL (P<0.001), and MCV decreased by 12.9 (6.8) fL (P<0.001). 67.6% children persisted to have anemia, albeit majority of them had mild or moderate anemia. There were no unsolicited side-effects reported. **Conclusion:** Sublingual methylcobalamin is effective for the treatment of **v**itamin B12 deficiency anemia in children; although, the duration of treatment needs to be longer than six weeks.

Keywords: *Homocysteine, Macrocytosis, Management, Nutritional anemia.*

Trial registration: Clinical Trial Registry of India: CTRI/2021/03/031845

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Vitamin B12 deficiency has been recognized as a significant health problem in children in India with nearly 25% of children aged 5-19 years having anemia due to vitamin B12 or folate deficiency [1]. Parenteral therapy is the preferred route for Vitamin B12 deficiency as it assures availability of the vitamin; although, oral vitamin preparations have also shown to be equally safe and effective when compared to parenteral vitamin B12 in adults [2,3]. However, given the uncertainty of absorption of vitamin B12 given orally due to interference by food or in the presence of underlying malabsorption, most physicians continue to prescribe parenteral vitamin B12 [4]. Sublingual route is being evaluated as an alternative to parenteral therapy as it bypasses the need for intrinsic factor for vitamin B12 absorption and is also convenient and cheap [5]. However, similar studies in children are scant [6-9]. We assessed the biochemical and hematological response to treatment with sublingual methylcobalamin among children with vitamin B12 deficiency.

METHODS

This prospective single-arm interventional study was conducted between November, 2020 and April, 2022 in the Department of Pediatrics, of a tertiary care hospital in Delhi, and the Department of Pediatric Hematology-Oncology of a teaching institute in Uttar Pradesh. The study protocol was approved by the institutional ethics com-mittees of the participating centers, and was registered with the Clinical Trials Registry of India.

Children presenting with anemia as defined by the World Health Organization [10] and macrocytosis [11] or findings suggestive of underlying vitamin B12 deficiency anemia on peripheral smear examination, were evaluated for underlying vitamin B12 deficiency anemia was defined as: serum cobalamin <200 pg/mL 2], and hemoglobin <11.5 g/dL in 1-5 years, or hemoglobin <11 g/dL in 5-12 years, and any one of: i) mean corpuscular volume (MCV) > 84+ [age (y) x 0.6] fL, ii) peripheral smear showing the presence of hypersegmented neutrophils (≥5 lobed nuclei in more than

5% of neutrophils) or macrocytes, or *iii*) bone marrow aspiration (BMA) suggestive of megaloblastic anemia.

Eligible participants were recruited consecutively after obtaining written informed consent from their parents or caregivers. Verbal assent was obtained for children aged 7-12 years. Children with neurological symptoms, critical illnesses, recent blood transfusion, chronic diseases, and those receiving hematinics, or drugs affecting vitamin B12 metabolism were excluded. Tests for complete blood counts and red cell indices were performed for all participants. A review of the peripheral smear for red cell size, fragmented cells, hypersegmented neutrophils, and the presence of thrombocytopenia was done. Serum cobalamin, ferritin, folate levels and homocysteine were estimated for all participants. Serum cobalamin levels were estimated by electrochemiluminescence immunoassay technique using Cobas e601 immunoassay analyzer, at baseline, day 10 and day 42 of treatment. Plasma homocysteine was estimated using enzyme-linked immunosorbent assay technique. Hyperhomocysteinemia was defined as plasma homocysteine >15 µmol/L. Severity of hyperhomocysteinemia was defined as moderate (15-30 µmol/L), intermediate (31-100 µmol/L) and severe (>100 µmol/L) [12].

Enrolled children were given a tablet methylcobalamin by sublingual route (Tablet MecobalOD 1500 µg, Rapross Pharma). The first dose was given under the direct supervision of the physician. Training of the parent(s) and the child was done by demonstrating the correct administration of sublingual methylcobalamin. The child was asked to drink a glass of water to avoid mouth dryness and after five minutes he was asked to hold the tablet under the tongue until it completely dissolved, given 20-30 minutes before breakfast. For children aged 2-6 years, if the child was unable to cooperate to take the medicine sublingually, the tablet was crushed and the powdered tablet was placed under the tongue. In children aged 7-12 years, one sublingual tablet was given every alternate day (five doses) while in children aged 1-6 years, three such doses were given. Thereafter, one tablet was given weekly and all children were followed up for six weeks. Compliance was checked by asking the parent to bring the empty blister pack of methylcobalamin tablets on follow-up visits. In case, a dose was missed, parent was asked to give the missed dose as soon as feasible. In case of concomitant iron deficiency, oral iron was given in a dose of 3 mg/kg/day of elemental iron (ferrous fumarate) and folic acid 5 mg/day for at least three months.

Hematological response and changes in serum cobalamin were assessed on day 10 and day 42 of treatment. Plasma homocysteine levels were measured at baseline and day 42 of treatment. On day 10, if serum cobalamin levels failed to rise >25% of baseline levels, or if on day 42, serum cobalamin levels were below 200 pg/mL, or if any child developed neurological symptoms during the study, the child was removed from the study and given parenteral rescue therapy.

Based on a previous study [6] wherein 129 children with vitamin B12 deficiency received sublingual vitamin B12, following which mean (SD) vitamin B12 increased from 146.7 (40.5) pg/mL to 565.5 (108.1) pg/mL, a sample size of two participants was calculated using Power Sample Size calculator software at 90% power and 5% type 1 error. Due to scant literature on the use of sublingual vitamin B12 in children, we considered our study as exploratory in nature and intended to recruit atleast 30 eligible patients during the study period, so that tests of significance could be applied.

Statistical analysis: Data were analyzed using SPSS software version 25 (IBM SPSS Inc). Descriptive statistics were used for nominal baseline characteristics. Categorical data were expressed as proportion, and continuous data were expressed as mean (SD). The change in continuous variables were analyzed by paired *t* test and categorical variables by Chi-square test. *P* value of less than 0.05 was considered as statistically significant.

RESULTS

Forty six children were enrolled, of which 9 children were lost to follow-up (**Fig. 1)**. The mean (SD) age of enrolled children was 8.2 (4.1) years, and 35.1% were males. The majority of enrolled children were vegetarians (75.7%), with 13.5% non-vegetarians.

The mean (SD) serum cobalamin levels rose significantly between day 0 and day 10 ($P<0.001$). The cobalamin levels on day 42 fell from that on day 10 ($P<0.001$) but were significantly higher than baseline ($P<0.001$). None of the children had cobalamin deficiency on day 10 and day 42. The mean (SD) hemoglobin levels at baseline, day 10 and day 42 are shown in **Table I**. Although, two children presented with hemoglobin levels of 3.4 g/dL and 4.6 g/dL each; none of the participants required blood component therapy. Following treatment, the mean (SD) hemoglobin increased by 1.1 (0.9) g/dL between day 0 and day 10 ($P<0.001$), while between day 10 and day 42, the mean (SD) hemoglobin increased by 1.1 (1.0) g/dL ($P<0.001$). Children with leukopenia, thrombocytopenia, and pancytopenia decreased significantly after 6 weeks of therapy (**Table I**). At the time of enrolment, 13.5% of the children had reticulocytopenia. The mean (SD) reticulocyte count (%) increased considerably between days 0 and day 10 ($P=0.002$), day 10 and 42 ($P=0.001$), and day 0 and day 42 ($P=0.01$). Five children (13.5%) had evidence of co-existent iron deficiency at initial presentation. None of the participants reported any side effects following the administration of sublingual methylcobalamin.

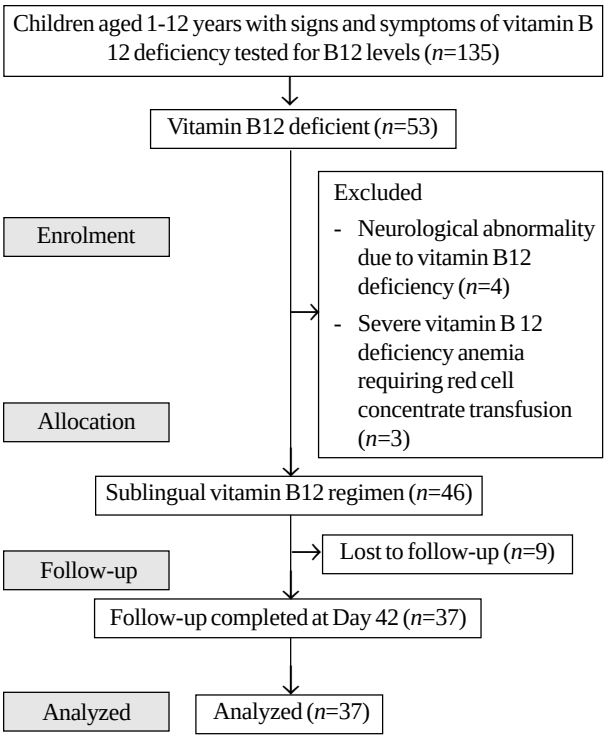

Fig. 1 Study flow chart.

Table I Laboratory Parameters of Children With Vitamin B12 Deficiency at Baseline, Day 10 and Day 42 (*N*=37)

Parameters	*Baseline*	*Day 10*	*Day 42*
Hemoglobin (g/dL)[a]	8.4 (2.1)	9.5 (2.1)	10.6 (1.7)
Mean corpusular volume (fL)[a]	102.8 (15.8)	96.2 (11.5)	89.9 (5.7)
Serum cobalamin levels (pg/mL)[a]	123.3 (35.8)	820.3 (451.3)	507.3 (274.2)
Plasma homocysteine levels (µmol/L)[a]	48.9 (17.8)	-	16.3 (8.5)
Grade of anemia[b]			
Mild anemia	6 (16.2)	9 (24.3)	8 (21.6)
Moderate anemia	15 (40.5)	16 (43.2)	16 (43.2)
Severe anemia	16 (43.2)	5 (13.5)	1 (2.7)
Pancytopenia	4 (10.8)	0	0
Leukopenia	11 (29.7)	7 (18.9)	2 (5.4)
Thrombocytopenia	14 (37.8)	4 (10.8)	0
Cobalamin deficiency	37 (100)	0	0
Hyperhomocysteinemia	37 (100)	-	17 (45.9)
Macrocytosis	32 (86.4)	28 (75.7)	23 (62.2)

Values expressed as no. (%) or [a]mean (SD). [b]Hemoglobin cutoffs in children: age 6mo-5y: mild anemia: 10-10.9 g/dL, moderate anemia: 7-9.9 g/dL, severe anemia: <7 g/dL; 5-12y: mild anemia: 11-11.4 g/dL, moderate anemia: 8-10.9 g/dL, severe anemia: <8 g/dL.

Hyperhomocysteinemia was found in all the enrolled children. None of the participants had severe hyperhomocysteinemia; 89.18% (*n*=33) had moderate hyperhomocysteinemia and 10.8% (*n*=4) had intermediate hyperhomocysteinemia. There was a significant decrease in mean (SD) plasma homocysteine levels between day 0 and day 42 (P<0.001).

DISCUSSION

In this single arm trial of 37 children, we found good biochemical response to subligual methylcobalamin as evident by normalization of cobalamin levels in all participants by day 10 of therapy. However, on day 42 there was a fall in serum cobalamin levels; although, none of the participants developed subnormal cobalamin levels. This may have been due to a decrease in dosing frequency of sublingual vitamin B12 used in the latter part of our protocol to weekly doses. Our findings are akin to previous studies [6,7], wherein cobalamin levels have shown complete normalization following intake by sublingual route in children. Both cyanocobalamin as well as methylcobalamin have been used by sublingual route [7,8].

The doses used in our study were extrapolated from doses of oral vitamin B12 used in children. In a study from northern India [13], a mean rise of 2.8 g/dL in hemoglobin was observed over a period of one month of daily oral vitamin B12 therapy (30 µg/kg/d). The daily dose of oral vitamin B12 in various studies has varied from 100 µg to 1000 µg [14-18], and the schedules followed were variable. The response to these vastly different doses can be explained by the fact that with increasing doses there is a diminished percentage absorption of orally administered vitamin B12 because of saturation of physiological intrinsic factor-mediated vitamin B12 absorption in the ileum. Similar pharmacodynamics for sublingually administered vitamin B12 have not yet been studied.

We witnessed that at 6 weeks, 67.6% of the children continued to be anemic. These findings are similar to those observed from a study using sublingual methylcobalamin, wherein nearly 64% of the children persisted to have anemia after one month of therapy [8]. Our results affirm that a longer duration of vitamin B12 therapy should be used in children with vitamin B12 deficiency anemia. Similar results were shown in certain other studies as well [6,14-16]. It has previously been reported that blood counts may take up to eight weeks to normalize [13]. We also noted that at 6 weeks follow-up, hyperhomocysteinemia persisted in nearly half the participants. It is recognized that plasma homocysteine is a good marker of functional vitamin B12 deficiency, although it may be elevated due to other causes like folate deficiency, hypothyroidism, renal failure, and certain genetic polymorphisms.

WHAT THIS STUDY ADDS?

- Sublingual methylcobalamin is effective in children aged 1-12 years with symptomatic vitamin B12 deficiency anemia.

A small sample size, short-term follow-up and lack of a comparator arm (oral or intramuscular) are the major limitations of our study. We also did not measure other markers of functional vitamin B12 deficiency like holotrancobalamin and methylmanic acid [2].

We conclude that sublingual methylcobalamin is effective and safe for treating symptomatic vitamin B12 deficiency anemia in children aged 1-12 years; although, the duration of treatment with vitamin B12 needs to be longer than six weeks.

Ethics clearance: Institutional Ethics Committee for Human Research, UCMS; No. IEC-HR/2020/PG/46/64-R1; IEC-HR/2021/51/6. IEC. Post Graduate Institute of Child Health, Noida; No. 2021-03-IM-14 dated Aug 14, 2021.
Contributors: CS: data collection, data analysis and draft preparation; SK: data analysis, draft preparation and revised the manuscript; PD: conceptualized the research, supervised the work, analyzed the data and gave critical inputs; SG: supervision of work, data analysis and critical inputs; RA, SS: laboratory work, data analysis and critical inputs; NR, MM: data collection, analysis and critical inputs. All authors approved final manuscript and are accountable.
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RESEARCH PAPER

Comparison of Emergency Severity Index Version 4 and Modified Pediatric Early Warning Score as Triage Models in the Pediatric Emergency of a Tertiary Care Public Sector Hospital

AASHIMA SOLANKI, PRERNA BATRA, VIKRAM BHASKAR, DEEPIKA HARIT
Departments of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi.

Correspondence to:
Dr Prerna Batra,
Director Professor,
Department of Pediatrics,
UCMS and GTB Hospital, Delhi.
drprernabatra@yahoo.com
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Objective: To identify the sensitivity of emergency severity index (ESI) version 4 and modified pediatric early warning score (PEWS) in identifying high urgency patients. **Methods**: This cross-sectional study was conducted between November, 2019 and October, 2021 in the pediatric emergency department of tertiary hospital in Delhi. 250 patients aged 0-12 years coming to pediatric emergency on pre-decided days for health-related complaints were enrolled. These were assessed with both triage systems within 30 minutes of their arrival by a single researcher. 'High urgency' patients were defined as the ones who either required admission in pediatric ICU or died or had critical value of vital parameters as per institution protocol. **Results**: ESI version 4 had a sensitivity of 95.5%, specificity of 80.3%, with AUC of 0.879 (95%CI 0.834-0.925) in identifying high urgency patients at levels 1 and 2. Modified PEWS had comparatively lower sensitivity of 79.1%, specificity of 97.8%, with AUC of 0.885 (95%CI 0.825-0.994) in identifying high urgency patients at score of ≥3. The ESI version 4 was found to be a better predictor of admission than the modified PEWS, with a sensitivity of 98.2%. Both the scores were able to identify patients at risk of mortality with a sensitivity of 100%. **Conclusion**: ESI version 4 is a better triage tool than modified PEWS in pediatric population in a tertiary care public hospital setting in this region.

Keywords: *Admission, Mortality, Readmission, Intensive care unit*.

Overcrowding of emergency department (ED) is a universal and ever-increasing problem. Attending patients in an unplanned manner in a crowded emergency department leads to delay in treatment of sick patients, while focusing on relatively stable ones. Chamberlain, et al. [1] found nearly 25% of admissions and over 1% of discharges from pediatric emergency were inappropriate decisions. Correct classification of high urgency patients is important as it ameliorates chaos and helps in managing patients in a more systematic manner.

World Health Organization (WHO) has given its WHO Emergency Triage, Assessment and Treatment (ETAT) system for identifying critically ill children in emergency for use in low resource settings at peripheral level [2]. At tertiary level, the Emergency Severity Index (ESI) is a five-level triage system that has been most widely used. This system accounts for both patient acuity and anticipated resource utilization. ESI version 4 is the most updated version [3]. On the other hand, modified pediatric early warning score (PEWS) is a 13-point clinical severity scale used to identify patients at risk of clinical deterioration [4]. Components include behavioral, cardiovascular and respiratory scores ranging from 0 to 13 with additional point to persistent vomiting and nebulization [4].

There are studies comparing several triage systems in pediatric population, but with variable results [5-7]. There is paucity of studies evaluating the performance of triage system separately for the children [8]. Thus, we planned this study with the primary objective of determining the sensitivity of ESI version 4 (levels 1, 2) in identifying high urgency patients and compared it with modified PEWS (≥3). Our secondary objective was to find the ability of the two triage tools to correctly identify patients who died and to identify low urgency patients who were discharged from hospital after being categorized as ESI level 5 and modified PEWS 0 and required hospital readmission.

METHODS

The study was conducted in a tertiary care teaching hospital from November, 2019 to October, 2022, after taking approval from the ethical committee of the institute. In our hospital, we run a separate emergency department for pediatric patients aged from 0 to 12 years. We tend to an average of 35,000-40,000 patients on yearly basis and

around 8000-10,000 patients get admitted out of this cohort per annum. Written informed consent was deferred for 30 minutes.

All the patients aged 0 to 12 years and coming to the pediatric emergency for health-related complaints were enrolled in the study during the work shifts of the principal investigator. Patients who were already intubated and coming to the facility, and hospital-to-hospital transfers were excluded from the study. Vital signs including respiratory rate, heart rate, percentage oxygen saturation (SpO2), and physical examination findings were noted, and patients were stabilized and managed as per protocols of the treating team. For the purpose of study, patients were assessed with ESI version 4.0 and modified PEWS within 30 minutes of their arrival by a single investigator, as per the standard methodology prescribed [9,10].

The participants were followed up at 6,12, 24, and 48 hours of presentation to emergency in terms of discharge from emergency, transfer to the ward, transfer to the high dependency unit (HDU)/pediatric intensive care unit (PICU), transfer to any other facility, death, and need of readmission within 48 hours after initial discharge from emergency [11]. All the details and outcomes were recorded in a predesigned case record form.

Aeichanbanjong, et al. [5] observed a sensitivity of 52% for identifying high urgency patients using ESI version 4.0 [5]. Taking alpha error of 5%, acceptable absolute difference of 10%, and prevalence of high urgency patients in our pediatric emergency as 40%, the sample size was calculated to be 240 using XLSTAT software. We decided to enroll 250 patients in the study.

Statistical analysis: The data were analyzed using SPSS version 20.0. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using unpaired *t* test, whereas the Manny-Whitney *U* test was used for discrete variables. Sensitivity, specificity, PPV and NPV were calculated to analyze the diagnostic accuracy of ESI version 4.0 and modified PEWS score in determining primary and secondary outcomes. A receiver operating curve (ROC) was drawn to determine the area under the curve (AUC). For all statistical tests, *P* value <0.05 was considered significant.

RESULTS

Baseline profile of patients enrolled in the study is shown in **Table I**. Majority (103, 41.2%) of the patients belonged to 7-12 years of age, followed by infants (78, 31.2%), and children aged 1 to 5 years (69, 27.6%). Majority of the patients had either a respiratory system complaint (28%) or gastrointestinal system complaint (28%), with 38 (15.2%) having multi-organ dysfunction. Patients in high urgency group had significantly higher respiratory rates, higher temperature and lower SPO2 at room air. Out of 250 patients presenting to ED, 11(4.4%) required life- saving intervention and 42(36%) patients had altered mental state or presence of distress. The number of resources utilized by patients were many in 179 (71.6%) cases.

Table I Baseline Characteristics of the Study Participants

Variable	*High urgency patients (n=67)*	*Low urgency patients (n=183)*
Male sex	38 (56.7)	98 (53.5)
Accompanied by parents	67 (100)	179 (97.8)
Transportation by		
Personal vehicle	67 (100)	181 (98.9)
Ambulance	0	2 (1.1)
Time taken to reach hospital		
<30 min	41 (61.2)	130 (71.1)
30 min-1 h	26 (38.8)	45 (24.6)
>1 h	0	8 (4.3)
Immunization status		
Immunized	57 (85.1)	165 (90.2)
Partially immunized	7 (10.4)	18 (9.8)
Unimmunized	3 (4.5)	0
Vital parameters[a]		
Respiratory rate[b]	53 (15)	29 (9)
Heart rate	144 (22)	112 (20)
SpO2[b]	90 (7)	97 (1)
Temperature[b]	100 (1)	99 (1)

All values in no. (%) or [a]mean (SD). [b]P<0.05. Patients who either needed admission to HDU/PICU or died within 48 hours of admission were considered as high urgency patients, while those who were discharged from emergency or shifted to the ward were considered low urgency.

Out of 250 patients enrolled, 67 (26.8%) were identified as high urgency patients based on outcome criteria. According to ESI version 4, 100 patients were identified as high urgency by their ESI levels 1 and 2, while modified PEWS (PEWS ≥3) identified only 57 patients as high urgency patients. ESI version 4.0 over-triaged 33% of the patients, whereas modified PEWS under-triaged 14.9 % of the patients as high urgency. ESI version 4 was observed to fare better for identification of high urgency patients than modified PEWS, while both were able to identify patients who died with 100% sensitivity. Modified PEWS was found to be more specific (96.6%) but not sensitive (38%) in predicting hospital admission in our study while ESI version 4.0 showed both good sensitivity (98.2%) and specificity (90.2%) in identifying the same. On comparing the performance of ESI version 4 and modified PEWS in identifying low urgency patients requiring hospital re-admission, modified PEWS had better sensitivity as

Table II Performance of Emergency Severity Index Version 4 and Modified Pediatric Early Warning Score for Identifying Various Outcomes in Children Presenting to the Emergency Department (*N*=250)

Score	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*AUC* (95% CI)
Identifying high urgency patients					
ESI level 1, 2	95.5%	80.3%	64%	98%	0.879 (834-0.925)
Modified PEWS ≥3	79.1%	97.8%	93%	92.7%	0.885 (0.825-0.994)
Identifying mortality					
ESI level 1, 2	100%	60.73%	3%	100%	0.804 (0.730-0.864)
Modified PEWS ≥3	100%	78.13%	5.26%	100%	0.891 (0.832-0.997)
Identifying hospital admission					
ESI level 1-4	98.2%	90.2%	74.7%	99.4%	0.729 (0.665-0.792)
Modified PEWS ≥3[a]	38%	96.6%	97.3%	32%	0.647 (0.575-0.712)
Identifying hospital readmission					
ESI level 5[b]	22.7%	75%	98.2%	1.6%	0.489 (0.162-0.763)
Modified PEWS 0[#]	63.8%	50%	98.7%	2.2%	0.569 (0.264-0.838)

[a]ESI level 1-4 and modified PEWS ≥3 were the patients who got admitted to the hospital; [b]ESI level 5 and modified PEWS 0 patients were managed on outpatient basis.

compared to ESI version 4 (63.8% vs 22.7%) (**Table II**). Both were able to identify high urgency patients (**Fig. 1a** and **1b**) (ESI version 4: AUC 0.879; 95% CI 0.834-0.925; modified PEWS: AUC 0.885; 95% CI 0.825-0.994) and mortality (**Fig. 2a** and **2b**) (ESI version 4: AUC 0.804; 95% CI 0.730-0.864; modified PEWS: AUC 0.891; 95% CI 0.832-0.997) with high area under curves.

DISCUSSION

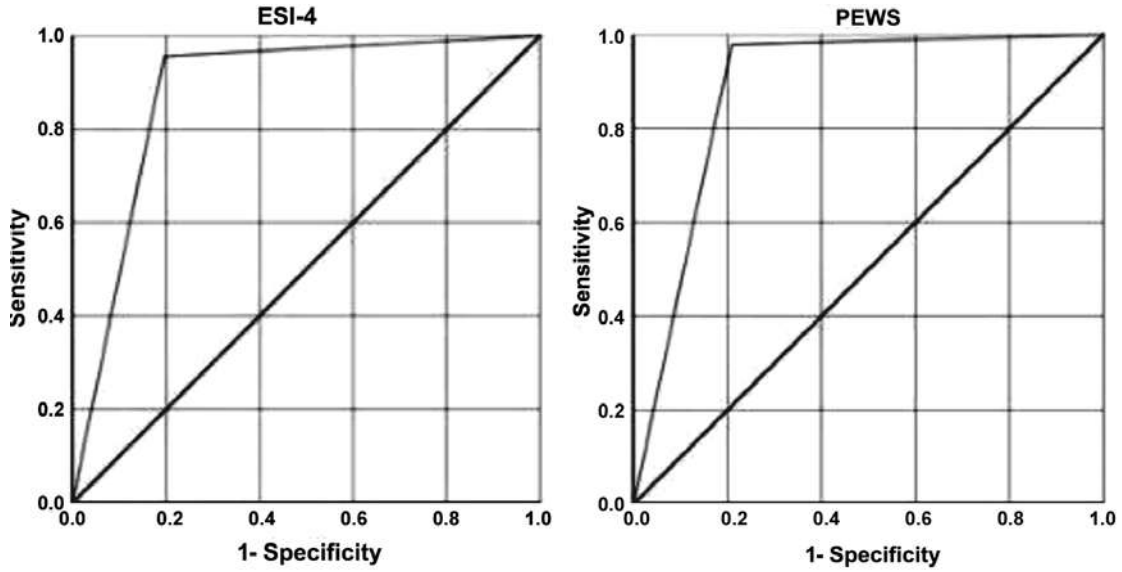
We observed that ESI version 4.0 was able to identify high urgency patients with better sensitivity as compared to modified PEWS and thus, is a better triage system in the pediatric emergency setting.

Bauman, et al. [12] conducted a prospective observational study for evaluation of ESI in pediatric patients. ESI level 1, 2 and 3 patients required multiple resources in 90% of cases in their study. Similar observations were echoed in our study, where the cohort of patients triaged to the highest three categories used an intermediate-to-high number of resources in 98.3% of cases.

The divergent definitions of normal and abnormal respiratory rate and pulse may explain some of the differences we found between modified PEWS and ESI version 4 triage levels. In particular, the fact that deviations from normal only affect the modified PEWS score while ESI version 4 escalates at any value higher than the reference, resulting in higher triage levels. This discrepancy has been reflected in total number of high urgency patients as defined by ESI version 4 than modified PEWS. Previous authors have also reported on the under- and over-triages by ESI version 4 within the pediatric population [13,14]. For a tool to be a better triage system, the percentage of under-triage should be as minimum as possible. Modified PEWS score was marred by under-triaging the high urgency patients to a percentage of 14.9%, with a comparatively low sensitivity of 79.1%. Similar results have been observed by Branes, et al. [15], where they compared PEWS with Rapid Emergency Triage and Treatment System pediatric (RETTS -P). The under-triage percentage was quite high for PEWS and there was lack of agreement between the two tools [15].

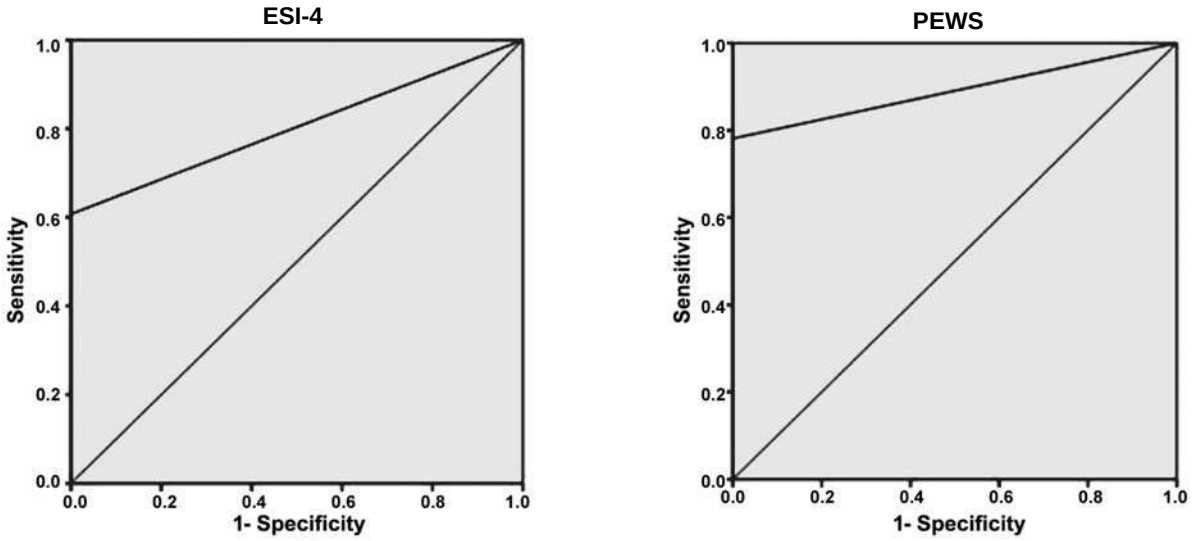
Other authors [3,5] have also used ESI for prediction of hospital admission among high acuity patients and found it to be a valid predictor. Modified PEWS was found to be specific but not sensitive in predicting hospital admission in our study, similar to the results by Lilitos, et al. [16]. Sieger, et al. [17] compared the validity of different PEWS for identification of need for ICU admission and found it to have moderate to good predictive ability [17].

The probability of dying in the ED was significantly associated with urgency categories in both triage systems. A comparable observation was made by Wuerz, et al. [18] who also followed up patients for a period of 6 months after the ED visit. A direct relationship with mortality rate and modified PEWS score has not been not studied till now but Akre, et al. [19] performed a retrospective study using a modified Brighton PEWS score similar to our study, and were able to identify children before a critical event with a sensitivity of 85%. Modified PEWS fared better than ESI version 4.0 for identifying patients requiring readmission after discharge from ED, though the number is too small to derive any conclusion. Solevag, et al. [4] observed read-mission in 14.7% of patients who were given a PEWS score of 0-2.



(*a*) (*b*)

Fig. 1 Receiver operating characteristic (ROC) curves depicting predictive ability of: (*a*) Emergency Severe Index (ESI) version 4, and (*b*) modified Pediatric Early Warning Score **(**PEWS) in identifying high urgency patients.



(*a*) (*b*)

Fig. 2 Receiver operating characteristic (ROC) curves depicting predictive ability of: (*a*) Emergency Severity Index (ESI) version 4, and (*b*) modified Pediatric Early Warning Score (PEWS) in identifying mortality.

A major limitation of our study is the lack of a standard pediatric triage tool, and thus, we used the actual outcome of patient as the gold standard. Further multi-centric trials are needed to make the results generalizable. Intra-observer and inter-observer agreements should also be assessed to test for reliability of the tool.

Ethics clearance: Institute Ethical Committee-Human Research; No. IEC-HR/2019/41/101R dated Oct 28, 2019.

Contributors: PB: conceived the idea; AS, PB: conceptualized the study and devised its design; VB, DH: provided critical inputs; AS: collected the data; PB,VB, DH: supervised data collection and helped in conduct of study; AS: drafted the manuscript. All authors have critically approved final version of

WHAT THIS STUDY ADDS

- Emergency Severity Index (ESI) version 4 has better sensitivity in identifying high urgency patient than modified Pediatric Early Warining Score (PEWS), and hence can be used as triage tool in the pediatric emergency department.

study as submitted, and agree to be accountable for all aspects of the study.

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RESEARCH PAPER

Postoperative Outcomes, and Growth and Brain Injury Outcomes in Spontaneous Intestinal Perforation vs Surgical Necrotizing Enterocolitis in Preterm Infants

PARVESH MOHAN GARG,[1,2] KATHERYN LETT,[2] MD ABU YUSUF ANSARI,[3] ISABELLA PITTMAN,[2] ROBIN RIDDICK,[2] NEHA VARSHNEY,[4] MICHAEL MORRIS,[5] DAVID SAWAYA,[5] CHARLOTTE TAYLOR,[6] KARTIK REDDY,[6] PETER PORCELLI,[1] WILLIAM HILLEGASS[3,7]

[1]*Department of Pediatrics/Neonatology, Atrium Health Wake Forest Baptist, Wake Forest School of Medicine, Winston Salem, North Carolina, USA.*
[2]*Department of Pediatrics/Neonatology, University of Mississippi Medical Center, Jackson, Mississippi, USA.*
[3]*Department of Data Sciences, University of Mississippi Medical Center, Jackson, Mississippi, USA.*
[4]*Department of Pathology, University of Mississippi Medical Center, Jackson, Mississippi, USA.*
[5]*Department of Pediatric Surgery, University of Mississippi Medical Center, Jackson, Mississippi, USA.*
[6]*Department of Radiology, University of Mississippi Medical Center, Jackson, Mississippi, USA.*
[7]*Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA.*

Correspondence to:
Dr Parvesh Mohan Garg,
Department of Pediatrics/ Neonatology,
Atrium Health Wake Forest Baptist,
Wake Forest School of Medicine,
Winston Salem, North Carolina, USA.
gargparvesh@hotmail.com
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Objectives: To compare the clinical outcomes in preterm infants following surgical necrotizing enterocolitis (sNEC) and spontaneous intestinal perforation (SIP). **Methods**: Retrospective comparison of clinical information in preterm infants with sNEC and SIP admitted between January, 2013 and December 31, 2018. The clinical outcomes were compared in two groups, including postoperative and brain injury detected on brain magnetic resonance imaging (MRI) after clinical and histopathological confirmation of the SIP and the NEC diagnosis. **Results**: 114 infants had sNEC, and 37 had SIP. Infants with SIP had lower median gestational age [25.1 weeks (23.5, 27.1) vs 26.6 (24.4, 31.0), *P*=0.03], an earlier mean (SD) age of disease onset [10.1 (11.3) days vs 19.6 (17.9); *P*<0.001] and lower maternal chorioamnionitis on placental pathology [4 (23.5%) vs 22 (68.8%); *P*=0.007), received more often Penrose drain therapy (54% vs 33%; *P*=0.03), had less median (IQR) bowel length loss [3.3 cm (1.72, 4.38) vs 21.4 (9.55, 35.3); *P*=<0.001] and had more often intact ileocecal valve (91.4% vs 65.7%; *P*=0.006] compared to those with sNEC. In addition, those with sNEC had lower median (IQR) weight *z* scores at the time of discharge [-1.88 (-2.80, -1.09) vs -1.14 (-2.22, -0.44); *P*=0.036] than SIP. There were no significant differences in postoperative ileus, duration of parenteral nutrition, surgical morbidity, length of stay, mortality, white matter, and grey matter injury on brain MRI at term equivalent age in preterm infants with SIP and sNEC. **Conclusion**: In our cohort, preterm infants with SIP and sNEC did not show significant differences in postoperative morbidity and brain MRI abnormalities at term equivalent age. sNEC had lower discharge weight *z* scores. Larger prospective studies are needed for confirmation of these findings.

Keywords: *Mortality, Outcome, Low birthweight.*

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Necrotizing enterocolitis (NEC) affects 6-10% of preterm infants with a birth weight of <1500 grams [1,2]. Despite advances in neonatal care, NEC and spontaneous intestinal perforation (SIP) remains a leading reason for surgical intervention and mortality in preterm infants [3-6,7,8]. Both conditions have the same surgical treatment, including Penrose drain or exploratory laparotomy with or without stoma formation.

A recent meta-analysis shows that mortality and neurodevelopmental outcomes were inconsistent between the studies of NEC vs SIP, with proper diagnostic criteria for cases with SIP [9]. Most of the studies lack the histopathological criteria for SIP diagnosis. Therefore, confirming the diagnosis of spontaneous ileal perforation during surgery on gross examination, without histopathological confirmation, is a challenge. Due to the lack of a consistent case definition of SIP and detailed evaluation of postoperative, growth, and white matter injury on brain magnetic resonance imaging (MRI) in previously published reports, there is a need for a comprehensive assessment of the clinical outcomes, including postoperative and brain injury outcomes detected on brain MRI after clinical and histopathological confirmation of

the SIP and the NEC diagnosis.

In this report, we sought to compare the postoperative, growth, and brain injury clinical outcomes in preterm infants with NEC and SIP in a predominantly African American cohort.

METHODS

This retrospective study was conducted at the University of Mississippi Medical Center (UMMC) Neonatal Intensive Care Unit after IRB approval at a Level IV unit with 900-1000 admissions yearly and referrals from the entire state. All infants with gestational age less than 37 weeks admitted between January 1, 2013 and December 31, 2018, with an NEC (Bell stage III)/SIP diagnosis were included in the study [10]. In this study, the SIP and SNEC diagnosis was confirmed clinically, and on the intestinal pathological examination. The white matter and grey matter injury were confirmed on the term equivalent brain MRI. Neonates diagnosed with medical NEC, kidney anomalies, congenital heart disease, and intestinal atresia were excluded from the analysis.

Demographic data collected included birth weight, gestational age, race, sex, mode of delivery, out born status, and Apgar score ≤6 at 5 min. Maternal information collected included chorioamnionitis, antenatal steroids, and pregnancy-induced hypertension (PIH). In addition, placental pathology was examined for gross and histologic findings based on the Amsterdam Placental Workshop Group Consensus Statement recommendations [11]. Clinical data included patent ductus arteriosus (PDA), frequency of PDA surgical ligation, duration of mechanical ventilation, dopamine use 24 hours following NEC/SIP onset, hematological information, ibuprofen/indomethacin treatment, and frequency of cholestasis (direct bilirubin ≥2 mg/dL) at any time after NEC diagnosis. Sepsis-related variables included blood culture-proven sepsis at NEC onset and duration/type of antibiotics.

NEC was defined using Bell criteria [10], and a diagnosis of NEC was made on abdominal *X*-ray findings, including portal venous gas, pneumatosis, and pneumoperitoneum. Bell stage III/surgical NEC frequency was gathered [10]. In addition, we recorded information on the age at NEC diagnosis and the fulminant NEC [12]. SIP infants (n=37) had pneumoperitoneum on an abdominal *X*-ray or perforation on intestinal pathology and less than 5 cm of bowel resected, with no necrosis or inflammation on the histopathology. At our center, preterm infants with pneumoperitoneum who weigh below 1 kg at NEC/SIP diagnosis and sick are treated first with a peritoneal drain but may later receive laparotomy based on clinical deterioration.

The modified neonatal staging criteria described in Improving Global Outcomes (KDIGO) Clinical Practice Guideline for acute kidney injury (AKI) was used to determine the incidence of kidney injury [13].

Postoperative information such as postoperative ileus days (defined as infants being nil per oral (NPO) after bowel surgery), time to reach full feeds (≥120 mL/kg/day), total parenteral nutrition days, length of stay, and hospital mortality were measured. We defined mortality as death due to any reason before hospital discharge. We also recorded information on intestinal failure (parenteral nutrition >90 days) and surgical morbidity. The surgical morbidity was classified as strictures, fistulas, wound dehiscence, surgical site infections (including abscesses), adhesions, and perforations.

Two pediatric neuroradiologists scored the MRI images independently, unaware of the infants' clinical course obtained at the corrected age of 36 weeks or before discharge. We used the scoring system reported by Woodward, et al. [14], which consists of eight 3-point scales. The categories of white matter abnormality were none (a score of 5 to 6), mild (a score of 7 to 9), moderate (a score of 10 to 12), and severe (a score of 13 to 15) [14].

Statistical analysis: Demographic and clinical factors in infants with surgical NEC and SIP were compared. We analyzed the continuous variables using the Mann-Whitney *U* test and summarized them with median (IQR). The categorical variables were tested across the outcome variable using the Chi-square test or Fisher exact test, as appropriate. A *P* value <0.05 was considered statistically significant for all analyses. All analyses were performed in R statistical software (version 4.2.1; The R Foundation for Statistical Computing).

RESULTS

In our study, we had data of 151babies, including 37 with SIP and 114 with sNEC. Of the 19 cases labelled as SIP by the surgery team; only 3 cases (15%) had met the histological criteria - 85% were NEC by histology. On the other hand, out of 132 cases labelled as surgical NEC by surgery team on looking at the bowel, 34 cases (25%) had met the SIP criteria.

The median (IQR) gestational age and birthweight of the population were 26.4 (24.3, 29.6) week and 780 (650, 1140) g, respectively. The preterm infants with SIP had lower median gestational age [25.1 (23.5, 27.1) vs 26.6 (24.4, 31.0) weeks; *P*=0.03], earlier age of disease onset [10.1 (11.3) vs 19.6 (17.9) days; *P*<0.001] and lower incidence of maternal chorioamnionitis on placental pathology [4 (23.5%) vs 22 (68.8%); *P*=0.007] compared to those infants with sNEC (**Table I**). The infants with SIP had received Penrose drain therapy more often [54% vs 33%; *P*=0.032], lost less bowel length (median (IQR) 3.3 cm (1.72, 4.38) vs 21.4 cm (9.55, 35.3); *P*<0.001] and retained the ileocecal valve more often [32 (91.4%) vs 71 (65.7%); *P*=0.006] compared to those with sNEC (**Web Table I**). Age of disease onset was 17.3 (I7)

Table I Baseline Characteristics of the Enrolled Infants (*N*=151)

Characteristics	*No.*	*NEC (n=114)*	*SIP (n=37)*
Maternal information			
Pregnancy-induced hypertension	141	28 (26.7)	12 (33.3)
Chronic hypertension	124	13 (14.3)	8 (24.2)
Chorioamnionitis	142	4 (3.77)	8 (22.2)
Maternal inflammatory response[a]	49	22 (68.8)	4 (23.5)
Fetal inflammatory response	49	13 (40.6)	2 (11.8)
High-grade villitis	48	5 (15.6)	0
Maternal vascular underproduction	49	16 (50.0)	13 (76.5)
Fetal thrombotic vasculopathy	48	1 (3.12)	0
Small for gestational age placenta	38	4 (17.4)	4 (26.7)
Large for gestational age placenta	38	2 (8.70)	0
Antenatal steroid use	136	65 (63.7)	24 (70.6)
Infant demographics			
Male	151	74 (64.9)	23 (62.2)
Ethnicity			
African-American		85 (75.2)	26 (74.3)
Caucasian		25 (22.1)	6 (17.1)
Other		3 (2.65)	3 (8.57)
Cesarean delivery	150	75 (66.4)	28 (75.7)
Outborn	151	78 (68.4)	19 (51.4)

Values in no. (%). No. indicate number of infants with available information. [b]P>0.05, [c]P<0.01. SIP: spontaneous intestinal perforation; NEC: necrotizing enterocolitis.

days for the whole study sample, and the median (IQR) length of bowel resected was 12.3 (4.27, 29.1) cm.

There were no significant differences in postoperative ileus days, duration of parenteral nutrition, surgical morbidity, length of stay, mortality white and matter, grey matter injury on brain MRI at term equivalent age in preterm infants with SIP and sNEC (**Table II** and **Web Table II**).Those with sNEC had lower median (IQR) weight *z* scores at the time of discharge [-1.88 (-2.80, -1.09) vs -1.14 (-2.22, -0.44); *P*=0.036] compared to those with SIP. There was no significant difference in weight, weight for length, head circumference, and length *z*-scores before NEC/SIP onset, four weeks following NEC, and before anastomosis in the two groups (**Web Table II, III** and **Fig. 1**).

DISCUSSION

In this study, infants with SIP were delivered preterm with almost ten days of difference in disease onset compared to sNEC infants, and lost less bowel length and retained ileocecal valve more often than those with sNEC infants. We found no significant differences in postoperative outcomes, mortality, length of stay, or white matter or grey matter injury in both groups.

Our previous retrospective observational cohort studies have reported the demographics, clinical outcomes, and systemic morbidities in preterm infants with NEC [15-19]. A previous retrospective cohort study in the Canadian neonatal network [20] also did not report any differences in mortality,

Table II Postoperative Outcomes in Infants With Spontaneous Intestinal Perforation and Necrotizing Enterocolitis

	No.	*Total (n=151)*	*NEC (n=114)*	*SIP (n=37)*	*p*
Postoperative intestinal features					
Postoperative ileus (d)[a]	145	17.6 (16.7)	17.8 (17.5)	17 (14.0)	0.82
Duration of parenteral nutrition (d)[b]	145	79 (38.0,117)	80 (38.5,116)	78 (32.8,1170)	0.98
Positive blood culture sepsis	149	44 (29.5)	36 (32.1)	8 (21.6)	0.31
Central line present (d)[b]	126	52 (29.0,83.8)	57 (27.5,86.0)	48 (29.5,74.0)	0.52
Duration of antibiotics (d)[b]	102	8 (6.00,12.0)	8 (5.0,13.0)	8 (7.0,10.0)	0.83
Cholestasis	116	72 (62.1)	56 (65.9)	16 (51.6)	0.24
Surgical morbidity	151	53 (35.1)	37 (32.5)	16 (43.2)	0.32
Wound dehiscence	151	21 (13.9)	13 (11.4)	8 (21.6)	0.20
Wound infection	151	10 (6.62)	9 (7.89)	1 (2.70)	0.45
Stricture	151	10 (6.62)	7 (6.14)	3 (8.11)	0.71
Adhesions	151	25 (16.6)	17 (14.9)	8 (21.6)	0.48
Discharge	151				0.92
Discharged		99 (65.6)	74 (64.9)	25 (67.6)	
Death		52 (34.4)	40 (35.1)	12 (32.4)	
Length of stay (d)[b]		117 (71,171)	116 (70.8,171)	120 (71,170)	0.87

Values in no. (%), [a]mean (SD) or [b]median (IQR).

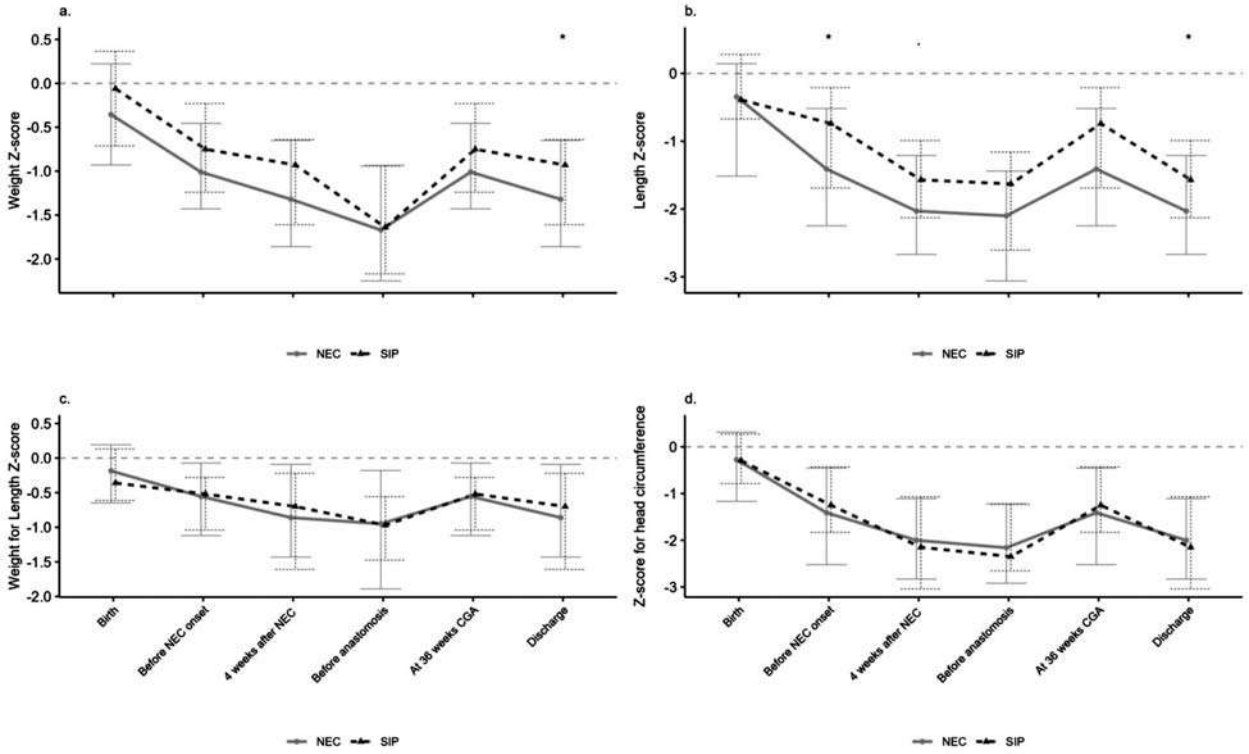

Fig. 1 Growth outcomes in babies with necrotizing enterocolitis vs babies with spontaneous intestinal perforation.

growth, and neurodevelopmental outcomes in groups comparing SIP and all sNEC cases, which is similar to our findings [20]. However, they reported higher mortality in infants with perforated surgical NEC cases compared to SIP cases. In our cohort, we did not divide our cases into the perforated or non-perforated NEC.

Like our findings of no significant statistical differences in brain MRI findings in the two groups, a study of the ELGAN cohort [21] also did not report any difference in neurodevelopmental outcomes in preterm infants with NEC and SIP. The authors reported higher white matter injury on head ultrasound in infants with NEC than SIP cases, and the MRI brain data were not provided [21].

A recent meta-analysis by Ang, et al. [9] of 18 cohort studies (13,606 infants), unadjusted ORs showed that SIP was significantly associated with increased odds of mortality, cerebral palsy, the composite outcome of death or disability, visual impairment, and hearing impairment. However, pooling of adjusted ORs (aOR) found significant associations only for mortality, severe disability, and the composite outcome of death or disability. The evidence level was judged as 'low' or 'very low' quality [9].

Our study's strengths include a detailed evaluation of the clinical, postoperative, and brain injury outcomes by brain MRI in preterm infants with sNEC and SIP. In addition, our study noted the non-agreement between the clinical and pathological diagnosis for the cases with SIP and whether infants with sNEC/SIP need an MRI brain at term equivalent age, which needs further evaluation in future studies.

Our study has important limitations. First, this was a single-center experience, reducing the study's generalizability. Our cohort infants were predominantly African American. While this is partly due to race distribution in Mississippi, this may also be related to adverse social determinants of health and genetic risk for NEC/SIP. Second, sample size limits our power to detect associations between clinical factors and outcomes. Our study also lacks data on hypotension, acid-base balance, and electrolyte data before the NEC/SIP onset, which may have affected brain injury outcomes. Finally, the small sample size coupled with multiple factors, outcomes, and comparisons may result in type I errors.

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Contributors: PMG: designed the study; PMG, KL, IP, MAYA, RR, CT, NV, MMR, DS, KR, PP, WBH: collected, analyzed the data and wrote the manuscript. All the authors contributed to and approved the manuscript.

WHAT THIS STUDY ADDS?

- Preterm infants with spontaneious intestinal perforation and surgical necrotizing enterocolitis were not found to have any significant differences in postoperative ileus days, duration of parenteral nutrition, surgical morbidity, length of stay, mortality, white matter or grey matter injury on brain MRI (at term equivalent age), which needs further confirmation in large prospective clinical studies.

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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Disease Features in Infants with Necrotizing Enterocolitis (NEC) and Spontaneous Intestinal Perforation (SIP)

	N	*Total (n=151)*	*NEC (n=114)*	*SIP (n=37)*	*P*
Age of disease onset (d)[a]	151	17.3 (17.0)	19.6 (17.9)	10.1 (11.3)	<0.001
Clinical presentation	148				0.09
Abdominal distension			94 (83.9)	35 (97.2)	
Bloody stools			10 (8.93)	0	
Feed intolerance			8 (7.14)	1 (2.78)	
Penrose drain	146		37 (33.6)	20 (54)	0.032
Fulminant necrosis	149		28 (25.0)	4 (10.8)	0.11
Presence of ileocecal valve	143		71 (65.7)	32 (91.4)	0.006
Jejunostomy	150		32 (28.3)	5 (13.5)	0.11
Ileostomy	150		50 (44.2)	23 (62.2)	0.09
Colostomy	150		7 (6.19)	4 (10.8)	0.47
Length of bowel resected (cm)[b]	140	12.3 (4.27, 29.1)	21.4 (9.55,35.3)	3.35 (1.72,4.38)	<0.001
Region of bowel resected	131				0.09
Large bowel or both			38 (38.0)	6 (19.4)	
Small bowel			62 (62.0)	25 (80.6)	
Length of jejunum lost (cm)[b]	131		0 (0;13.1)	0 (0;0.80)	0.012
Length of ileum lost (cm)[b]	140		5.50 (0;15.0)	1.00 (0;3.80)	0.001
Length of colon lost (cm)[b]	137		0 (0;2.50)	0 (0;0)	0.05
Total small bowel lost (cm)[a]	150		19.1 (20.8)	3.29 (3.46)	<0.001
Residual small bowel (cm)[a]	150		88.5 (29.0)	85.9 (25.2)	0.6
Residual colon (cm)[a]	150		25.6 (9.91)	26.1 (6.20)	0.7
Hemodynamic variables					
Assisted ventilation (intubated)	127				
Intubation			81 (87.1)	29 (85.3)	
CPAP			5 (5.38)	2 (5.88)	
High flow			2 (2.15)	1 (2.94)	
Room air			5 (5.38)	2 (5.88)	
Patent ductus arteriosus	149		63 (56.2)	26 (70.3)	0.19
PDA surgical ligation	146		5 (4.50)	3 (8.57)	0.40
Pressor support 24 h after NEC/SIP	145		83 (75.5)	26 (74.3)	0.99
Indomethacin use	146		15 (13.6)	6 (16.7)	0.86
Apgar score <6 at 5 min	146		26 (23.9)	15 (40.5)	0.08
AKI by serum creatinine	133		55 (57.3)	21 (56.8)	1.00
AKI by urine output	133		46 (47.4)	12 (33.3)	0.21
Platelet transfusion before NEC/SIP onset	142		82 (75.2)	24 (72.7)	0.95
Blood transfusion before NEC/SIP onset	127		87 (93.5)	32 (94.1)	0.99
CRP at 24 h after NEC/SIP onset[b]	101	8.70 (3.40;18.6)	13.1 (4.40;19.3)	3.20 (1.78;8.27)	0.004
CRP at 2 wk after NEC/SIP onset[b]	81	3.40 (1.60;5.80)	4.00 (1.75;7.20)	2.25 (1.33;4.35)	0.041

Values in no. (%) or [a]mean (SD) or [b]median (IQR)AKI: acute kidney injury, CRP: C-reactive protein, PDA: patent ductus arteriosus.

Web Table II Brain Magnetic Resonance Imaging Findings, and Outcomes in Infants With SIP and NEC (N=151)

Brain MRI Findings	*N*	*All patients*	*NEC (n=114)*	*SIP (n=37)*	*P*
MRI corrected gestational age at MRI	69	40.5 (38.2; 46.2)	40.0 (38.0; 47.3)	41.2 (40.4; 45.6)	0.45
White matter abnormality	69	36 (52.2)	27 (55.1)	9 (45.0)	0.62
White matter abnormality	69				0.72
Normal		33 (47.8)	22 (44.9)	11 (55.0)	
Mild		17 (24.6)	14 (28.6)	3 (15.0)	
Moderate		13 (18.8)	9 (18.4)	4 (20.0)	
Severe		6 (8.70)	4 (8.16)	2 (10.0)	
White matter signal abnormality	69				0.93
Normal		41 (59.4)	28 (57.1)	13 (65.0)	
Mild		14 (20.3)	11 (22.4)	3 (15.0)	
Moderate		14 (20.3)	10 (20.4)	4 (20.0)	
Loss of periventricular volume	68				0.79
Grade 1		34 (50.0)	23 (47.9)	11 (55.0)	
Grade 2		28 (41.2)	20 (41.7)	8 (40.0)	
Grade 3		6 (8.82)	5 (10.4)	1 (5.00)	
Extent of any cystic abnormality	68				0.64
Grade 1		52 (76.5)	38 (79.2)	14 (70.0)	
Grade 2		11 (16.2)	7 (14.6)	4 (20.0)	
Grade 3		5 (7.35)	3 (6.25)	2 (10.0)	
Ventricular dilation	68				0.87
Grade 1		34 (50.0)	24 (50.0)	10 (50.0)	
Grade 2		26 (38.2)	19 (39.6)	7 (35.0)	
Grade 3		8 (11.8)	5 (10.4)	3 (15.0)	
Thinning of corpus callosum	68				0.93
Grade 1		35 (51.5)	24 (50.0)	11 (55.0)	
Grade 2		26 (38.2)	19 (39.6)	7 (35.0)	
Grade 3		7 (10.3)	5 (10.4)	2 (10.0)	
Grey matter abnormality	68				0.41
Normal		61 (89.7)	44 (91.7)	17 (85.0)	
Abnormal		7 (10.3)	4 (8.33)	3 (15.0)	
Extent of grey matter signal abnormality	67				0.41
Grade 1		59 (88.1)	42 (89.4)	17 (85.0)	
Grade 2		6 (8.96)	3 (6.38)	3 (15.0)	
Grade 3		2 (2.99)	2 (4.26)	0 (0)	
Quality of gyral maturation	68				0.41
Grade 1		60 (88.2)	43 (89.6)	17 (85.0)	
Grade 2		6 (8.82)	3 (6.25)	3 (15.0)	
Grade 3		2 (2.94)	2 (4.17)	0 (0)	
Loss of subarachnoid space	67				0.32
Grade 1		55 (82.1)	40 (85.1)	15 (75.0)	
Grade 2		10 (14.9)	5 (10.6)	5 (25.0)	
Grade 3		2 (2.99)	2 (4.26)	0 (0)	

Sip: Spontaneous intestinal perforation; NEC; Necrotozing enterocolitis.

Web Table III NEC vs SIP Growth Parameters at Different Time Points Before and Following the NEC Onset

At birth	*N*	*Total (N=123)*	*NEC (N=91)*	*SIP (N=32)*	*p*
Weight (z score)	123	-0.33 (-0.96;0.33)	-0.38 (-1.00;0.24)	-0.06 (-0.75;0.42)	0.16
Total length (cm, median (IQR))	123	33.0 (30.5;37.8)	33.0 (30.5;39.0)	32.5 (30.5;35.9)	0.54
Total length (z score)	123	-0.38 (-1.19;0.21)	-0.37 (-1.42;0.16)	-0.39 (-0.77;0.46)	0.22
Weight and total length (percentile)	123	39.7 (23.6;58.7)	39.7 (22.1;59.7)	39.2 (27.0;56.5)	0.77
Weight and total length (z score)	123	-0.26 (-0.72;0.24)	-0.23 (-0.74;0.30)	-0.36 (-0.68;0.16)	0.84
Head circumference (cm, median (IQR))	123	23.5 (21.5;26.6)	23.5 (21.6;27.5)	22.5 (21.5;24.2)	0.18
Head circumference (z score)	123	-0.30 (-1.04;0.27)	-0.31 (-1.11;0.17)	-0.30 (-0.84;0.35)	0.44
Before NEC		*n*=123	*n*=90	*n*=33	
Weight (z score)	123	-0.97 (-1.38; -0.39)	-1.00 (-1.43; -0.50)	-0.75 (-1.27; -0.19)	0.11
Total length (cm, median (IQR))	123	36.0 (33.0;40.0)	36.0 (33.4;40.9)	35.0 (32.5;38.0)	0.22
Total length (z score)	123	-1.07 (-2.04; -0.28)	-1.14 (-2.16; -0.30)	-0.74 (-1.69; -0.28)	0.18
Weight and total length (percentile)	123	26.5 (12.2;45.8)	25.2 (12.1;44.3)	30.2 (12.6;53.7)	0.41
Weight and total length (z score)	123	-0.63 (-1.17; -0.15)	-0.71 (-1.21; -0.18)	-0.52 (-1.13;0.09)	0.24
Head circumference (cm, median (IQR))	123	25.5 (23.4;29.2)	26.0 (23.6;29.8)	25.0 (22.0;27.2)	0.12
Head circumference (z score)	123	-1.38 (-1.94; -0.34)	-1.40 (-2.06; -0.33)	-1.25 (-1.85; -0.35)	0.59
4 weeks after NEC		*n*=104	*n*=74	*n*=30	
Weight (z score)	104	-1.21 (-1.81; -0.65)	-1.29 (-1.84; -0.65)	-0.92 (-1.57; -0.64)	0.37
Total length (cm, median (IQR))	104	40.0 (35.9;43.7)	40.0 (36.6;44.0)	38.0 (35.1;41.8)	0.06
Total length (z score)	104	-1.76 (-2.55; -1.01)	-1.90 (-2.62; -1.03)	-1.55 (-2.12; -1.00)	0.26
Weight and total length (percentile)	104	19.8 (7.38;44.4)	18.8 (7.47;44.3)	26.8 (7.03;43.3)	0.45
Weight and total length (z score)	104	-0.84 (-1.44; -0.11)	-0.88 (-1.41; -0.10)	-0.62 (-1.50; -0.17)	0.58
Head circumference (cm, median (IQR))	104	28.0 (25.5;30.7)	28.6 (26.2;32.0)	26.0 (23.6;29.4)	0.010
Head circumference (z score)	104	-2.05 (-2.84; -1.05)	-1.98 (-2.79; -1.09)	-2.13 (-3.00; -0.94)	0.61
Before reanastomosis		*n*=89	*n*=61	*n*=28	
Weight (z score)	89	-1.66 (-2.23; -0.90)	-1.69 (-2.25; -0.87)	-1.60 (-2.15; -0.95)	0.81
Total length (cm, median (IQR))	89	45.0 (42.0;48.5)	45.5 (42.0;49.0)	44.4 (42.4;47.0)	0.49
Total length (z score)	89	-1.91 (-3.02; -1.06)	-2.06 (-3.06; -1.05)	-1.62 (-2.55; -1.13)	0.42
Weight and total length (percentile)	89	17.9 (3.24;42.4)	18.2 (2.89;48.2)	17.2 (6.65;32.5)	0.91
Weight and total length (z score)	89	-0.92 (-1.85; -0.19)	-0.91 (-1.89; -0.04)	-0.95 (-1.39; -0.46)	0.9
Head circumference (cm, median (IQR))	89	31.0 (29.2;33.5)	31.2 (30.0;33.5)	31.0 (28.5;33.1)	0.51
Head circumference (z score)	89	-2.04 (-2.68; -1.05)	-2.04 (-2.78; -1.05)	-2.16 (-2.64; -1.17)	0.86
@ 36 weeks		*n*=102	*n*=74	*n*=28	
Weight (z score)	102	-1.25 (-2.00; -0.74)	-1.30 (-2.00; -0.72)	-1.22 (-1.96; -0.78)	0.92
Total length (cm, median (IQR))	102	42.5 (40.0;44.5)	42.1 (40.0;45.0)	43.0 (40.6;44.0)	0.76
Total length (z score)	102	-1.71 (-2.74; -1.09)	-1.83 (-2.94; -0.84)	-1.48 (-2.60; -1.26)	0.93
Weight and total length (percentile)	102	16.4 (4.34;42.8)	16.2 (4.00;43.3)	16.5 (9.38;34.6)	0.8
Weight and total length (z score)	102	-0.98 (-1.72; -0.18)	-0.98 (-1.75; -0.16)	-0.96 (-1.32; -0.40)	0.8
Head circumference (cm, median (IQR))	102	30.0 (28.7;31.6)	30.0 (29.0;32.0)	29.4 (28.4;31.0)	0.36
Head circumference (z score)	102	-1.72 (-2.62; -0.74)	-1.71 (-2.55; -0.48)	-1.98 (-2.69; -1.08)	0.33
Discharge		*n*=99	*n*=70	*n*=29	
Weight (z score)	99	-1.76 (-2.63; -0.83)	-1.88 (-2.80; -1.09)	-1.14 (-2.22; -0.44)	0.036
Total length (cm, median (IQR))	99	51.5 (49.5;56.9)	52.0 (49.5;56.4)	51.1 (48.6;62.2)	0.64
Total length (z score)	99	-1.70 (-3.03; -0.68)	-1.88 (-3.34; -0.94)	-1.07 (-1.95; -0.36)	0.08
Weight and total length (percentile)	99	32.2 (5.30;77.8)	31.0 (4.93;80.9)	40.6 (13.5;77.4)	0.85
Weight and total length (z score)	99	-0.54 (-1.65;0.76)	-0.54 (-1.75;0.88)	-0.66 (-1.10;0.75)	0.86
Head circumference (cm, median (IQR))	99	35.5 (33.8;38.0)	36.0 (33.8;38.0)	35.0 (34.0;38.0)	0.69
Head circumference (z score)	99	-2.01(-2.88; -0.90)	-1.97 (-2.94; -0.87)	-2.15 (-2.71; -1.05)	0.92

RESEARCH PAPER

Determining the Spinal Canal Depth in Neonates Using Bedside Ultrasonography

NIDHI GUPTA, HA VENKATESH, RAJATH PEJAVER, CHERRY GARG, KARTHIK NAGESH
Department of Neonatology, Manipal Hospital, HAL, Old Airport Road, Bengaluru, Karnataka.

Correspondence to:
Dr. HA Venkatesh,
Department of Neonatology,
Manipal Hospital, HAL,
Old Airport Road, Bengaluru,
Karnataka.
venkatveena46@gmail.com
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Objective: To provide a gestation age- and weight-specific mathematical formula for predicting the optimal depth of spinal needle insertion. **Methods**: The study included 127 neonates between 28 and 40 weeks of gestation and weighing 700 to 4000 grams, and a total of 202 ultrasound examinations were performed. Anterior and posterior borders were delineated using ultrasound and measured as spinal canal depth in lateral decubitus position at L3- L4 vertebral interspace. The mid-spinal canal depth (MSCD) was calculated. **Results**: Spinal canal dimensions showed an increasing trend with an increase in weight and post-menstrual age of the babies. The best correlation was found between weight and MSCD with an r^2 of 0.85, which is given by the formula MSCD (cm) = 0.2 X weight in kg + 0.45.**Conclusion**: Knowledge of the spinal canal depth using the formula may facilitate accurate needle placement, thereby decreasing traumatic lumbar puncture.

Keywords: *Accuracy, Lumbar puncture, Mid-spinal canal depth, Traumatic.*

The lumbar puncture is a commonly performed procedure in the neonatal intensive care unit (NICU). The diagnosis of meningitis is based on cerebrospinal fluid (CSF) analysis. Up to 50% of CSF samples obtained from neonates may be blood-stained and difficult to interpret [1], leading to injudicious use of antibiotics. Moreover, repeated attempts for a lumbar puncture may compromise the neonate physiologically. Any intervention aimed at reducing the incidence of traumatic or failed lumbar puncture may add to improved neonatal management and care [2]. Ultrasound-guided lumbar puncture is one such modality to determine the depth of the spinal canal for a safe procedure.

Prior knowledge of the distance from the skin to the middle of the spinal canal (mid-spinal canal depth, MSCD) may be useful in assessing how far the needle should be inserted. Less is known about spinal canal depth in low birth weight and very low birth weight neonates. There is no standard reference to help a physician judge the depth of insertion of a lumbar puncture needle. Many formulae have been given based on various anthropometric parameters including age, height, weight, and body surface area, or combinations of these, to calculate the optimal depth of lumbar puncture needle insertion in various age groups of the patient population [1, 3, 4, 5]. Determining the needle length using bedside ultrasound not only helps in tapping the CSF successfully, but also to customize the needle length for different weights and gestational ages.

METHODS

The study was done between Feburary, 2022 and December, 2022, after institutional ethics committee clearance. Neonates between 28 weeks to 40 weeks of gestation, weighing 700 grams to 4000 grams were enrolled, and those with major musculo-skeletal anomalies, or spinal or lumbosacral anomalies (spina bifida, sacral dimples, or pits) were excluded.

Weight and gestational age were recorded in all infants fulfilling the inclusion criteria. Gestational age was assigned as per the last menstrual period or corrected expected delivery date (c-EDD). Ultrasonography (USG) was performed using Philips CX-50 Machine with a curvilinear probe frequency of 5-8 Hertz. The examination was performed with the infant nursed in lateral decubitus position. Ultrasound measurement was obtained at L3-L4 vertebral interspace, identified by palpation from the 12th thoracic vertebra counting downwards. The baby's vitals were continuously monitored during the procedure. Anterior and posterior borders were delineated, and we measured anterior spinal canal depth (ASCD) and posterior spinal canal depth (PSCD) viz., ASCD, the distance from the skin to the anterior wall of the spinal canal; PSCD, the distance from the skin to the posterior wall of the spinal canal; and spinal canal thickness=ASCD×PSCD (**Fig. 1**). The mid-spinal canal depth was calculated as PSCD + (Spinal canal thickness/2).

To assess intra-observer agreement, the principal investigator took two readings independently; for inter-

observer agreement, a senior neonatal consultant trained in USG took measurements independently. The intra-class correlation coefficient was calculated for agreement.

Based on the previous literature for an outcome variable on correlation between baby weight in grams and spinal depth with the minimum correlation of 0.50 (50%) in the study domain, 95% statistical power, 5% level of the type of I error (α) and 5% type of II error rate (β), the sample size of 100 was calculated as adequate.

Statistical analysis: Collected data were entered into Excel software and analyzed using R software version 4.0.2. The intra-class correlation was calculated to evaluate the inter-rater reliability of continuous measurements. A scatter plot was constructed to visualize the relationship between two continuous variables. A simple linear regression line was fitted to establish the relationship between two continuous variables. The coefficient of determination r^2 was also reported for the regression model. *P* value less than 0.05 was considered statistically significant.

RESULTS

A total of 202 USG examinations were performed on 127 neonates (125 males). The mean post-menstrual age of the study group was 34 weeks 5 days (range 28 weeks 4 days - 40 weeks 6 days), and mean weight at the time of examination was 1877 grams (range 820-4000 grams). The best correlation was found between weight and MSCD with an r^2 (coefficient of determination) of 0.85, which is given by the formula MSCD (cm) = 0.2W (Kg) + 0.45 (**Fig. 2**). The correlation between various spinal depths and weight is demonstrated with the help of a scatter plot and the formula is derived from a simple linear regression equation.

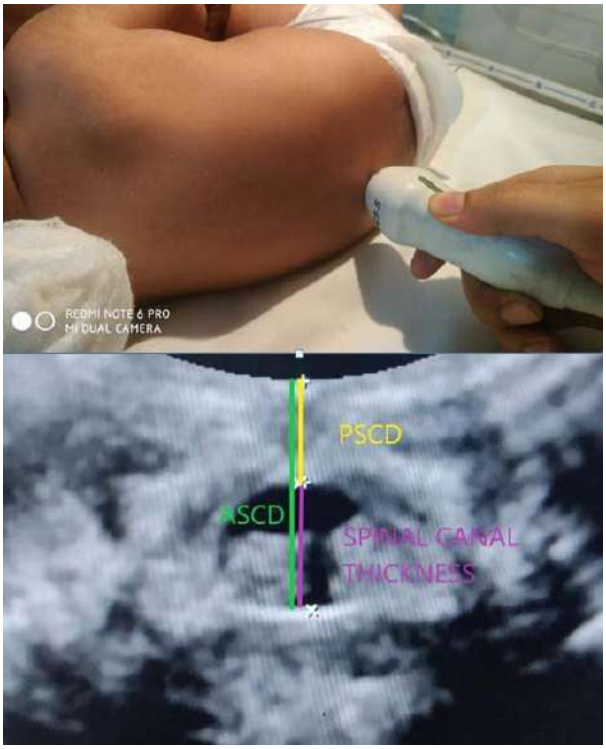

Fig.1 (*a*) Ultrasound probe placement, and (*b*) Ultrasound image showing measurement of anterior spinal canal depth, posterior spinal canal depth, and spinal canal thickness.

On the linear regression model, the coefficient of determination of post-menstrual age came out to be maximum with ASCD (**Fig. 3**). Though, there was a positive correlation for all three spinal canal parameters with post-menstrual age, the r^2 value was found to be significantly

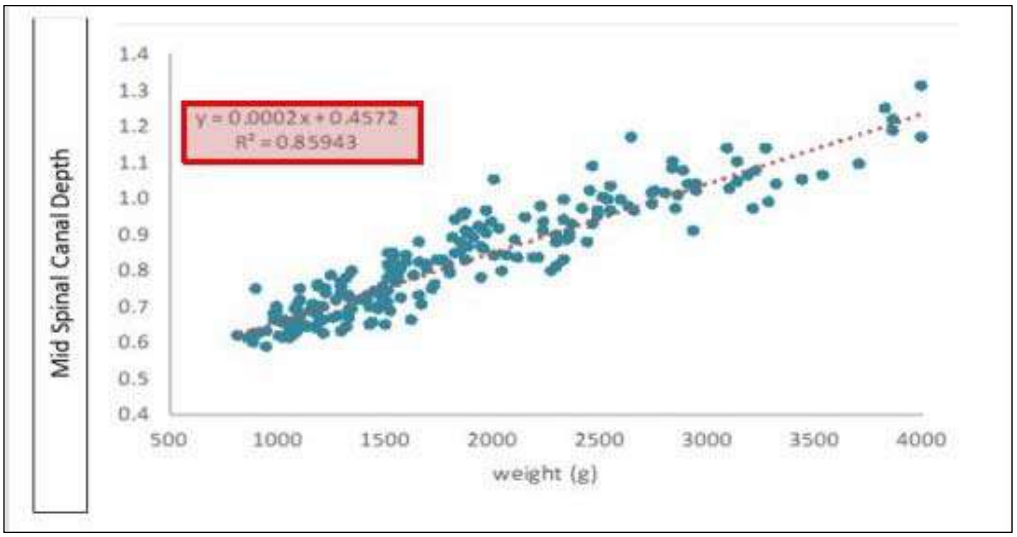

Fig.2 Scatter plot demonstrating the linear correlation between mid-spinal canal depth (MSCD) and weight.

Table I Intra-Rater and Inter-Rater Reliability in the Study (*N*=202)

Ultrasound reading	*Interclass correlation (95% CI)*		
	ASCD	*PSCD*	*MSCD*
Rater I, reading 1 vs reading 2	0.981 (0.975-0.986)	0.939 (0.920-0.954)	0.962 (0.947-0.972)
Rater I, reading 1 vs Rater II	0.981 (0.976-0.986)	0.921 (0.897-0.939)	0.953 (0.937-0.963)
Rater I, reading 2 vs Rater II	0.983 (0.978-0.987)	0.940 (0.922-0.954)	0.960 (0.952-0.970)

ASCD: anterior spinal canal depth; PSCD: posterior spinal canal depth; MSCD: mid-spinal canal depth.

lower as compared to the weight. Inter-rater reliability was used to measure the level of agreement between two observers. Interclass correlation was calculated which represents good reproducibility (**Table I**).

DISCUSSION

In our study, the body weight had a linear relationship with all the spinal canal measurements when compared to the postmenstrual age, and relevant formula derived. These formulae may help the less experienced physicians to tap the CSF successfully. The best correlation was found between body weight and mid-spinal canal depth.

Bonadio, et al. [3] demonstrated that the depth of the lumbar puncture necessary to obtain clear CSF best correlated with the body surface area. However, body surface area is not a routine parameter used in the neonatal population. Subsequently, a few studies [6-8] were performed for assessing the relationship between skin-epidural distance and various anthropometric variables. However, these studies examined needle insertion distance to epidural space, which may not be the true representation of the CSF containing subarachnoid space. Craig, et al. [4] provided height as the best guide for predicting optimum LP needle insertion depth. Height is more easily measured in older children but the same does not apply to sick neonates, as weight is relatively easier to measure. Shenkman, et al. [5] were probably among the first to use ultrasonographic measurements in a study of premature and former premature infants. Arthurs, et al. [1] did an ultrasound-based study and demonstrated a good correlation between MSCD and weight in the neonatal population and a nomogram and formula developed. This formula varies from ours because our study comprised more of the VLBW and LBW population with the median weight at the time of ultrasound examination being 1.69 kg as compared to the median weight of 2.46 kg in their study [1]. Furthermore, the units used for spinal canal depth in their study were mm, while we used cm. A randomized control trial [2] performed for validating the nomogram did not show significant improvement in overall lumbar puncture success rates. However, it was observed that using a depth marker on an lumbar puncture needle before insertion using a nomogram can significantly improve lumbar punc-

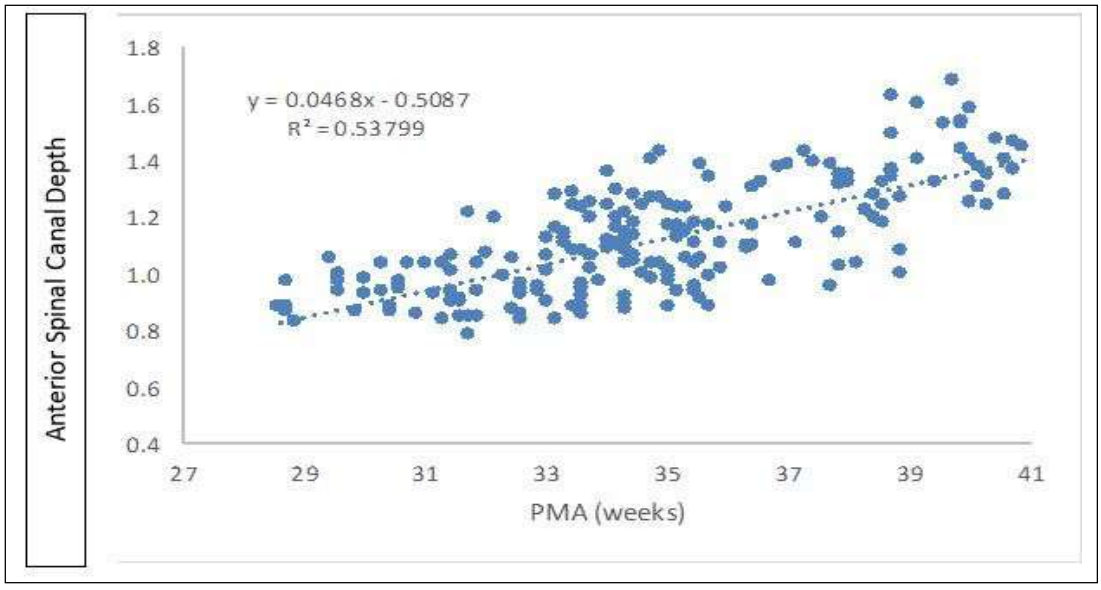

Fig.3 Scatter plot demonstrating the linear correlation between anterior-spinal canal depth (ASCD) and postmenstrual age.

WHAT THE STUDY ADDS?

- The best correlation was found between body weight and mid-spinal canal depth (MSCD) given by the formula; MSCD in cm = 0.2 x weight (kg) +0.45.

ture success rates in premature (28-37 weeks gestation) infants, and also when lumbar puncture was performed by less experienced doctors. The number of very low birth weight infants in this RCT was too small to be able to demonstrate any significant effect of the technique on the incidence of traumatic lumbar punctures. An MRI-based study on post-mortem fetuses including extreme preterm and VLBW babies in large numbers was also done; though, post-mortem changes associated with loss of cutaneous fluid were not accounted for [9]. Another limitation of their study was that MRI is traditionally performed in a supine position whereas lumbar puncture is typically performed in the left lateral position.

Our study has a few limitations. The ultrasound beam direction was kept perpendicular to the spinal canal in the midline while taking measurements. The difference in angulation of approach during lumbar puncture in contrast to the perpendicular distance may result in an error. Similarly, a paramedian approach would also increase the needle insertion distance.

All of our ultrasound measurements were taken in the curved lateral position, which is the standard position for lumbar puncture. Weight is a routinely measured parameter in neonates; hence, our formula can be easily used in daily practice.

We provide a formula that may be more robust for the prediction of spinal depth in VLBW and LBW neonates, especially in Indian neonates. We believe that the formula developed in this study has high reliability for the Indian population. Futher studies to validate the formula would help in guiding the neonatologists for the best formula for spinal canal depth in the neonate.

Ethics clearance: Ethical Committee of Manipal Hospital, Bengaluru; No. MHB/01/220950/90, dated Feb 12, 2022.
Contributors: NG: Acquisition, primary analysis and interpretation of results, HAV: conceptualized the study, taught and supervised ultrasound skills and revised the manuscript, RP: provided critical inputs in the revision of the article, CG: literature search, drafted the primary manuscript, KN: provided critical inputs in the revision of the article.
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RESEARCH PAPER

Effect of Comorbidity-free Neonatal Hypoglycemia on Neurodevelopment at 18 Months of Age: A Prospective Cohort Study

ASHFAQ MASOOD,[1] FARHEEN QURESHI,[2] PARVEZ AHMED,[1] MASOOD UL HASSAN,[3] IMTIYAZ ALI[4]

[1]*Department of Pediatrics, Government Medical College, Srinagar, Jammu and Kashmir.*
[2]*Department of Gynaecology and Obstetrics, Government Medical College, Srinagar, Jammu and Kashmir.*
[3]*Department of Neonatology, Sher I Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir.*
[4]*Department of Community Medicine, Sher I Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir.*

Correspondence to:
Dr Ashfaq Masood, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir.
dr.sayyidashfaq@gmail.com
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Objective: To study the impact of neonatal hypoglycemia on neurodevelopment and neurodevelopmental clusters at 18 months of age. **Methods**: This prospective cohort study was conducted at the pediatric and neonatal wards of a tertiary care hospital. Study subjects were neonates with hypoglycemia (blood sugar <47 mg/dL at presentation). Enrolled babies were evaluated at 3,6,9,12 and 18 months for overall neurodevelopment and neurodevelopmental clusters by Developmental Assessment Scale for Indian Infants (DASII). **Result**: Of the total 259 neonates with hypoglycemia, 92 met the inclusion criteria, and 85 babies could be evaluated at 3,6,9,12 and 18 months. 20 (23.5%) neonates had asymptomatic hypoglycemia, and 7 (8.2%) had symptoms with seizures. 17.6% (*n*=15) babies had delayed development quotient for development at 3 months of life. At 18 months of age, 9.4% (*n*=8) subjects had delayed development quotient for motor clusters and 7% (*n*=6) had delayed development quotient for mental clusters. Positive correlation was found between age and both improvement in motor development (*r*=0.99, *P*<0.05) and mental development (*r*=0.95, *P*<0.05) clusters. **Conclusion**: Motor and mental developmental clusters are affected by neonatal hypoglycemia. Improvement in developmental clusters occurs with increasing age.

Keywords: *Developmental delay, Follow-up, Screening, Outcome.*

Neonatal hypoglycemia is a common clinical entity [1]. Transient hypoglycemia is common during metabolic transition to extra uterine life in term neonates [2], and is unrelated to nutrition [3]. There is no universal consensus about the safe blood sugar level for newborn infants, partly because individual susceptibility to brain injury varies with factors like gestational age, birth weight, presence of comorbid conditions and the ability of the infant to produce and use alternate cerebral fuels [4]. Presently most guidelines focus to keep blood sugar level above 2.5 mmol/dL (>45 mg/dL) [5,6]. Multiple studies have confirmed neurodevelopmental delay associated with neonatal hypoglycemia [7].

While assessment of neurodevelopmental clusters is a better way of assessment of individual motor and mental development, hence studying longitudinally and analyzing individually these clusters at different ages will give insight in neurodevelopment delay. There is a paucity of literature pertaining to impact of comorbidity-free neonatal hypoglycemia on neurodevelopmental status. We studied the association of neonatal hypoglycemia in relation to neurodevelopment in comorbidity-free neonates.

METHODS

This is a hospital based prospective study conducted from 1 October, 2016 till 31 May, 2019 at the pediatrics and neonatology departments of one of the tertiary care centers of Jammu Kashmir, and enrolled neonates referred from different maternity centers in urban and rural areas of the region between 1 October, 2016 and 30 November, 2017. The study was approved by the institutional ethics committee. All term and late preterm neonates (>34 weeks gestational age) with weight appropriate for gestation and having documented hypoglycemia (<47mg/dL) were included in the study. The blood glucose estimation was done by bed side glucometric strip method and then confirmed by glucose oxidase enzymatic method using fluoride containing tubes [8].

We excluded those neonates that had comorbid factors that could affect neurodevelopment as cofounding factor viz., infants born to mothers with overt diabetes, intra-uterine infections like TORCH, documented perinatal asphyxia, neonates with congenital anomaly or suspected chromosomal abnormality, life threatening events like intracranial bleeds, severe sepsis and meningitis, hyperbilirubinemia

needing exchange transfusion or other conditions affecting neurodevelopment like prematurity or low birth weight below 2500 grams. For this, antenatal, intrapartum and postnatal records were analyzed. At birth, Apgar score, birth weight and gestation [9] were assessed and recorded. Record was also made of symptomatic hypoglycemia, degree of hypoglycemia, age at which hypoglycemia was observed, mode of delivery, and the catchment area. Sepsis screen, metabolic abnormalities, congenital anomalies, and thyroid profile were assessed.

Enrolled babies were re-evaluated at 3, 6, 9, 12 and 18 months for overall neurodevelopment and 11 neuro-developmental clusters by Developmental Assessment Scale for Indian Infants (DASII), an Indian adaptation of Bayley Scale of Infant Development [10]. Neurodevelopment and neurodevelopmental clusters were analyzed as development quotient (DQ). Record of development quotient in motor and mental developmental clusters was recorded as: <70 (delayed), 70-79 (low optimal), 80-99 (optimal), ≥100 (high optimal). Neuroimaging was considered in patients with delayed development at any stage during follow-up.

Table I Demographic, Clinical, Laboratory and Neuro-developmental Profile of Neonates With Comorbidity-free Hypoglycemia Enrolled in the Study (*N*=85)

Characteristics	*Delayed development at 18 months*	
	Motor domain	*Mental domain*
Male sex, *n*=45	4 (4.7)	3 (3.5)
Urban residence, *n*=72	7 (8.2)	5 (5.8)
Cesarean delivery, *n*=64	5 (5.8)	5 (5.8)
Gestation 34^1-37^0 wk, *n*=23	5 (5.8)	3 (3.5)
Gestation >37^1-42^0 wk, *n*=62	3 (3.5)	3 (3.5)
Birth weight 2500-4000 g, *n*=71	8 (9.4)	6 (7)
Birth weight 4001-4500 g, *n*=14	-	-
Hypoglycemia		
Symptomatic, *n*=65	8 (9.4)	6 (7)
Asymptomatic, *n*=20	-	-
Symptomatic with seizures, *n*=7	7 (8.2)	6 (7)
Blood sugar		
<30 mg/dL, *n*=15	1 (1.1)	1 (1.1)
30-40 mg/dL, *n*=37	5 (5.8)	4 (4.7)
>40 mg/dL, *n*=36	2 (2.2)	1 (1.1)
Documentation of hypoglycemia		
Age <1 h, *n*=1	-	-
Age 1-2 h, *n*=13	-	-
Age 2 -6 h, *n*=26	2 (2.2)	1 (1.1)
Age >6 h to 5 d, *n*=41	4 (4.7)	3 (3.5)
Age >5 d, *n*=4	2 (2.2)	2 (2.2)

All values in no. (%).

Statistical analysis: The data recorded were compiled and entered into a Microsoft Excel spreadsheet. Continuous variables were expressed as means and categorical variables were summarized as percentages. Correlation coefficients were calculated using Microsoft Excel version 2019. Chi-square test was applied for comparison of various categorical variables. *P* value less than 0.05 was considered statistically significant.

RESULTS

Of the 1940 newborns referred to our unit, 259 cases were observed to have blood sugar <47 mg/dL but 167 cases were excluded because of other risk factors for neurodevelop-mental injury, thereby leaving a final cohort of 92 cases for follow-up. Of these, data of 85 cases (without comorbid factors) were analyzed, as seven babies were lost to follow-up. The various demographic, clinical and biochemical parameters in relation to delayed neurodevelopment are shown in **Table I**.

At 3 months of age, 15 babies (17.65%; 95%CI 10.23%-27.43%) had delayed overall neurodevelopment (DQ<70) in both the motor and mental domains. The rest 70 babies (82.3%) had low optimal, optimal and higher optimal range of normal neurodevelopment. These 15 babies were evaluated for four motor and seven mental developmental clusters. Among motor clusters, neck control (NC), body control (BC) and locomotion skills (LS) were impaired in all, and reaching and manipulation skills (RMS) in 8 (53.3%) babies. Among mental clusters, reaching manipulation exploring (RME), social and imitative behavior (SIB), understanding surroundings (US), and memory (M) were impaired in all 15 babies with delayed overall neurodevelop-ment. Of the other mental clusters, visual cognizance (VC) was impaired in 9 (60%), language and vocalization skill (LVS) in 8 (53.3%), and auditory cognizance (AC) in 2 (13.3%) babies (**Web Table I**). At 18 months of age, only 8 (9.4%) babies had impaired motor development, and 6 (7%) babies had impaired mental development (**Web Table I**).

At 3 months, Among 70 babies with no delayed overall neurodevelopment (DQ ≥70), 19 cases (27.1%) had low optimal development in all mental developmental clusters, and only in RMS in motor development cluster. At 18 months, 16 babies (22.8%) had low optimal development in mental clusters (sparing the AC) and 7 (10%) had low optimal development in motor.

There was a negative correlation (r=-0.99; P=0.001) of age with impaired /delayed neurodevelopment in those with delay, and a positive correlation (r =0.639; P=0.24) of age with number of patients with optimal development (**Fig. 1**).

Fifteen subjects underwent magnetic resonance imaging (MRI) of the brain at 15-18 months of age; 40% (*n*=6) cases

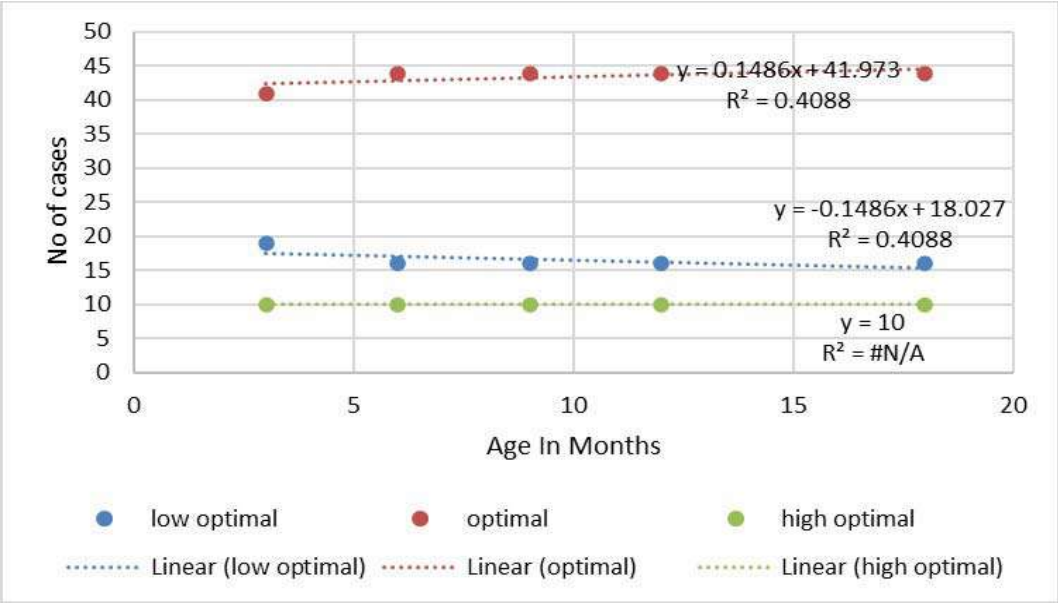

Fig. 1 Correlation between normal development and age in months.

had hyperintensities in the parieto-occipital region of the brain.

DISCUSSION

This study on prospective evaluation of neurodevelopment among comorbidity-free neonatal hypoglycemic showed that 17.8% cases had neurodevelopmental delay at third month of life. On follow-up at 6,9,12 and 18 months, these cases (8.4% cases in motor and 10.8% in mental) showed improvement to sub optimal range; although, 9.4 % and 7% cases were still having impaired motor and mental development, respectively. The other 82.2% cases with normal (sub optimal) neurodevelopment at third month of life on follow-up also showed improvement to optimal and higher optimal range by18 months (73.4% in motor and 63.4% in mental); however, 8.2% and 18.8% cases in this group still had low optimal range in motor and mental development, respectively. Significantly delayed motor and mental clusters of development in severe symptomatic hypoglycemia, especially those with seizures and sustained hypoglycemia, was observed.

Neurodevelopmental delay in neonatal hypoglycemia observed in our study is a substantiation of already known facts [7,11-13]. Majority of the studies have already attributed the role of comorbid risk factors in association with neonatal hypoglycemia for brain injury and neurodevelopmental delay [14-16]. Some studies have also observed the role of associated co-factors like severe symptomatic hypoglycemia and sustained hypoglycemia and delayed neurodevelopment [17,18]. There is scarcity of literature regarding neurodevelopment in neonatal hypoglycemia in the first year of life. Two previous studies [19,20] have shown neurodevelopmental delay in as high as 50-60% in neonatal hypoglycemia at three months of age; however, the cases in their studies had other comorbid factors that could impair neurodevelopment and thus the results may not be comparable to our study.

Although, neonatal hypoglycemic brain injury has been observed to involve predominantly the posterior portion of the occipito-parietal region of the brain [11], yet no consensus has been evolved for uniform diagnostic criteria in neonatal hypoglycemic brain injury outcome [12]. Lucas, et al. [21] observed that recurrent moderate hypoglycemia in preterm newborns can lead to severe motor and mental developmental delay when followed till 18 months of age. Annept, et al. [22], in a retrospective observational study at 6-9 years of age, observed that without risk factors the neurodevelopment can be normal except low optimal motor function. Ansell, et al. [14] evaluating the neonatal hypoglycemia cases till 2 years observed no neurodevelopmental delay. Babies with neonatal hypoglycemia did not have any major developmental delay, except low optimal development across five executive functions at 4.5 years [23].

Our study has certain limitations. DASII being a clinical scale for neurodevelopment, visual testing like visual evoked potential (VEP) and auditory function testing like oto-acoustic emissions (OAE) and brainstem evoked response audiometry (BERA) need to be performed separately in

WHAT THIS STUDY ADDS

- Neurodevelopmental delay at third month of life was seen in 17.8% babies with comorbidity-free neonatal hypoglycemia.

these patients. A major strength of our study was the exclusion of most comorbidities associated with abnormal neurodevelopment, and description of various impaired developmental clusters due to co morbid free hypoglycemic brain insult.

In conclusion, the neurodevelopmental delay in hypoglycemia cases can be profound if associated with severe symptomatic hypoglycemia and sustained hypoglycemia with equal effect on motor and mental domains. Improvement in neurodevelopment occurs with advancing age but improved developmental clusters still remain the sub optimal range.

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Ethics clearance: IEC, Govt. Medical College, Srinagar; No. 122/ETH/GMC/ICMR dated March 30, 2017.
Contributors: AM: principal investigator; FQ: antenatal information of patients' mothers; PA: concept about the study; MuH: technical interpretation of neurodevelopmental scale; IA: final compilation of manuscript and statistical support. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
Funding: None; *Competing interests*: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Delayed Motor and Mental Developmental Clusters at Various Stages of Follow-up in Babies With Comorbidity-free Neonatal Hypoglycemia (*N*=85)

Age in months	*Clusters of mental development*							*Clusters of motor development*			
	VC	*AC*	*RME*	*SIB*	*LVS*	*UR*	*M*	*NC*	*BC*	*RMS*	*LS*
3	9	2	15	15	8	15	15	11	15	8	15
6	8	2	11	9	8	11	11	8	13	7	13
9	5	0	8	7	8	10	10	8	12	7	8
12	5	0	6	7	6	8	8	1	8	7	8
18	5	0	6	6	6	6	6	0	8	6	8

NC:neck control; BC:body control; RMS:reaching and manipulation skills; LS:locomotion skills; VC:visual cognizance; AC:auditory cognizance; RME:reaching manipulation and exploring; LVS:language vocalisation skills; SIB:social imitative behavior; US:understanding of surroundings; M:memory.

RESEARCH PAPER

Seroprotection With Three Dose vs Four Dose Schedule for Hepatitis B Vaccination in Children Living With Human Immunodeficiency Virus: Follow-up Data at 36-42 Months From a Randomized Controlled Trial

NISHA YADAV,[1] POOJA DEWAN,[1] SUNIL GOMBER,[1] BINEETA KASHYAP,[2] RICHA GUPTA[3]

[1]Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi.
[2]Department of Microbiology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi.
[3]Department of Pathology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi.

Correspondence to: Dr. Pooja Dewan, Professor, Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi 110095.
poojadewan@hotmail.com
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Objective: To compare the long-term seroprotection (anti-HBs ≥10 IU/L) in children living with HIV (CLHIV) receiving a 3- or 4-dose double-strength (20 µg) recombinant Hepatitis B virus (rHBV) vaccination. **Methods**: We present anti-retroviral therapy (ART) clinic based follow-up data collected from January, 2021 to August, 2022, from CLHIV who had received either 3-dose or 4-dose double-strength (20 µg) rHBV vaccination, after 36-42 months and assessed for anti-HBs titres, naïve and memory T-helper lymphocytes, CD4 counts and HIV viral load. Children found unprotected after primary immunization, were administered a single double-strength rHBV vaccine booster dose (20 µg) and seroprotection was reassessed after 4 and 12 weeks. **Results**: Out of 50 children initially vaccinated, 45 were followed up 36-42 months after primary immunization; median (IQR) anti-HBs titres (IU/L) were 230 (80.5 - 305.7) in the 3-dose group (*n*=23) and 263.5 (47.1-332.9) in the 4-dose group (*n*=22) (*P*=0.33). 19 and 20 children in the 3-dose and 4-dose group, respectively, were seroprotected (*P*=0.24). Anti-HBs titres at 36-42 months correlated with CD4 counts at baseline, anti-HBs titres at 1 and 6 months after completion of primary immunization and percentage of memory T-helper lymphocytes. All the five children (3-dose group: 4; 4-dose group: 1) who received rHBV vaccine booster dose attained seroprotection one-month later. **Conclusion**: Three-dose double strength rHBV vaccination schedule offers comparable seroprotection to a 4-dose double strength rHBV vaccination schedule in CLHIV receiving ART.

Keywords: *Anti-HBs titre, Booster, Immunity, Vaccine.*

Hepatitis B virus (HBV) and Human Immunodeficiency Virus (HIV) share common risk factors and modes of transmission. The global prevalence of HBV–HIV co-infection among HIV-infected individuals is 7.4% [1]. Children living with HIV (CLHIV) are particularly vulnerable to hepatic disease if coinfected with HBV.

Suboptimal seroconversion has been reported with hepatitis B vaccine (HBV) in HIV-infected adults and children [2]. Seroprotection following hepatitis B vaccination wanes over time and this is often accelerated in people living with HIV (PLHIV) [3]. Several strategies have been explored to boost seroconversion rates such as the use of double doses, additional doses, combination vaccines and adjuvants [4,5].

The Infectious Diseases Society of America recommends a 3-dose schedule of double strength (20 µg) HBV vaccine in CLHIV [6]. National Institutes of Health [7] and Advisory Committee on Immunization Practices, (Centre for Disease Control, USA) [8] recommends a 3-dose schedule of 10 µg recombinant HBV vaccine (rHBV) for HIV-infected children. Indian Academy of Pediatrics (IAP) [9] recommends vaccination of symptomatic CLHIV with 4-dose schedule (0, 1, 2, and 6 months) of 20µg rHBV vaccine, and three doses (0, 1, and 6 months) in asymptomatic CLHIV. There is no consensus regarding the best schedule of dosage and strength for primary hepatitis B vaccination in CLHIV. Further, whether long-term seroprotection following administration of 4 doses of rHBV vaccine is better than that offered with 3 doses is not known. An earlier study comparing primary immunization with either 3 or 4 double-strength doses of rHBV vaccine in CLHIV showed immediate seroprotection rates both groups were statistically comparable [10]. In the current study, we compared the longterm seroprotection in the same study population after 36-42 months.

METHODS

This prospective cohort study was conducted from January, 2021 to August, 2022 in the anti-retroviral therapy (ART)

clinic, in the Department of Pediatrics, of tertiary level hospital. Written informed consent was obtained from caregivers of the participants. Approval was obtained from the Institutional Ethics Committee–Human Research (IEC-HR (IECHR/2020/PG/46/68-R1).

Fifty children from our previous study [10], who had been randomized using block randomization technique to receive either a 3-dose HBV vaccine (0, 1, 6 months) or a 4-dose (0,1,2,6 months) double strength (20µg) HBV vaccination and were available for follow-up were enrolled. These children were followed up 36-42 months after completion of primary HBV vaccination and anti-HBs titres were estimated using ELISA-based kits (Bioneovan Co., Ltd, Beijing, China). Seroprotection response (responders) to HBV vaccination was defined as anti-HBs titres ≥10 IU/l. Those who had anti-HBs tires ≥100 IU/l were labelled as "good responders." Children with anti-HBs titres <10 IU/l were labelled as non-responders. CD4 counts and naïve (CD4CD45+ RA+) and memory (CD4CD45+RO+) T-helper lymphocytes were measured using flow cytometry (®Beckmann Coulter). Memory and naive T-helper lymphocytes (%) in both the groups were compared with healthy age-matched controls (n=25). Healthy age-matched controls were recruited from amongst the non-HIV infected siblings of CLHIV attending the ART Clinic. HIV load was estimated using RNA PCR technique. Children found unprotected, were given a single booster dose of rHBV vaccine (Biological E Limited, Telangana, India) and reassessed at 4 and 12 weeks for anti-HBs titres. Parameters like age, sex, ART regimen, CD4 counts and viral load were retrieved from records of the patient available at the ART Centre.

Study outcome variables: We evaluated anti-HBs titers and the proportion of CLHIV who were seroprotected 36-42 months after completion of primary hepatitis B vaccination in both groups. The anti-HBs titres following administration of a single double strength booster were also estimated.

Statistical analysis: SPSS software package version 25 was used. The median inter-quartile range, (IQR) was calculated

Table I Baseline Characteristics of Study Participants

	3-dose Group (n=23)	*4-dose Group (n=22)*	*P value*
Age (mo)	124 (87-162)	182.5 (145.5-185.25)	0.001
Duration of ART (mo)	65 (55-92)	80 (67.25-113.25)	0.05
Anti-HBs at 7 mo (IU/L)	128 (35-165.6)	250 (175.9-303)	0.001
Anti-HBs at 12 mo (IU/L)	166.6 (48.4-250)	214 (145.7-257)	0.22
CD4 at primary immunization (/mm^3)	1046 (721-1244)	858.5 (653.5-1190)	0.28
CD4 at 36-42 mo (/mm^3)	1022 (777-1324)	686.5 (509-1014)	0.45
VF at 36-42 mo[a]	3 (13)	3 (13.6)	0.70
Anti-HBs titres at 36-42 mo (IU/L)	230 (80.5-305.7)	263.5 (47.1-332.9)	0.33
Seroprotected children[a]			
At 7 mo	20 (80)	24 (96)	0.19
At 12 mo	22 (88)	24 (96)	0.61
At 36-42 mo	19 (82.6)	20 (91)	0.24
Good responder at 36-42 mo[a]	17 (73.9)	16(72.7)	0.82

Values in median(IQR) or [a]no.(%). Anti-HBs: antibody to hepatitis B surface antigen, CD: clusters of differentiation, VF: virological failure.

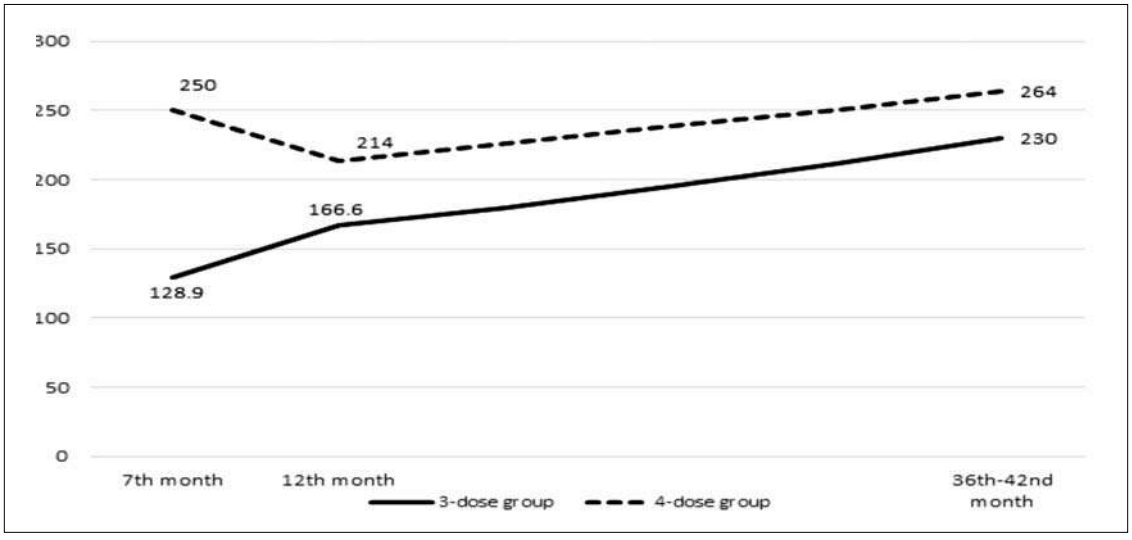

Fig. 1 Trend of median anti-HBs titres (IU/l) over time in the study participants.

Table II Memory and Naïve Helper T-lymphocytes Estimated by Flow cytometry in the Study Participants

	3-dose group (n=21)	*4-dose group (n=19)*	*Control (n=25)*
Memory T-helper lymphocytes	20.8 % (7-31.7)	11.9 % (2-25.3)	30.9 % (19.9-37.6)
Naïve T-helper lymphocytes	57.6 % (52.8-62.4)	58.9 % (54.8-63.7)	57.4 % (54.1-72.9)

Values expressed as median (IQR).

for anti-HBs titres, age, CD4 count, HIV RNA copies, and T-cell subpopulations and compared between groups using Mann-Whitney *U* test. Proportion of seroprotected children, non-responders and good responders to booster were compared using Chi-square test. Fischer's exact test was used wherever necessary. Spearman correlation coefficient was used to measure strength of association.

RESULTS

A total of 45 children (3-dose group: 23, 4-dose group: 22) were included. Demographic characteristics and other parameters in both groups are depicted in **Table I**. **Fig. 1** depicts the trend of anti-HBs titres following primary vaccination. The difference in proportions of seroprotected children between the two groups at various time points were statistically insignificant. Naïve and memory T-helper lymphocytes were estimated in 40 patients (3-dose group: 21, 4-dose group:19) and compared with healthy control group as shown in **Table II.**

The anti-HBs titres at 36-42 months follow up had a significant correlation with CD4 counts at the time of primary immunization (r=0.34, *P*=0.02), anti-HBs titres at 1 and 6 months after completion of primary immunization (7th and 12th month after starting primary immunization) (*r*=0.45, *P*=0.002; *r*=0.7, *P*<0.001 respectively), CD4 count at 36-42 months after completion of primary immunization (*r*=0.49, *P*=0.001) and percentage of memory T-helper lymphocytes (*r*=0.8, *P*<0.001).

Five out of six cases did not show seroprotection at 36-42 months after primary HBV vaccination, and were administered a booster dose. One of these six children was lost to follow-up. Four out of six of these children had virological failure.

DISCUSSION

We assessed the longevity of response to rHBV vaccination in CLHIV and its correlation with the number of doses of HBV vaccine received during primary immunization (3- vs 4-dose), immunological status of the participants (CD4 counts, proportion of naïve and helper T-lymphocytes) and HIV viral load. At 36-42 months follow up, the seroprotection rates were comparable in the 3-dose and 4-dose HBV vaccine groups. Surprsingly, the proportion of responders in the 4-dose group had fallen over time (although statistically insignificant) while that in the 3-dose group showed a marginal increase. The fall in seroprotection rates in the 4-dose group may have been due to the lesser gap between the second and third rHBV doses compared to that in the 3-dose group (1-month *vs* 5-month gap). Previously, it has been established that seroprotection rates are affected by increasing the time interval between the second and third dose of HBV vaccine [11]. Similar to our results, Launay, et al. [12] had reported that compared to the standard 3-dose HBV vaccination schedule, the proportion of responders after 4-dose double dose schedule had steadily fallen over time (82% at 7th month; 77.5% at 18 months; 72.4% at 30 months; 71% at 42 months) in HIV-infected adults, although the longterm seroprotection offered by a 4-dose vaccination schedule was better. Unlike our study where all children were receiving ART, they reported that among the responders, 81% and 100% were on ART in 3-dose group and 4-dose group respectively; while among non-responders only 39% and 15% were on ART in 3-dose and 4-dose group respectively. Pessoa, et al. [13] revealed that children who received 3-doses of hepatitis B vaccination (*n*=8) had long-term (at ≥4 years of primary vaccination) seroprotection rates of 37.5% against 41.7% after four doses (*n*=12), 52.8% after five doses (*n*=14) and 66.6% after six doses (*n*=6). The seroconversion rates in our study at 12 months and 36 months follow up were greater than those in the aforementioned studies. The fact that every child in our study received consistent ART may be a significant contributing factor.

Anti-HBs titres at 7th and 12th month had a strong correlation with anti-HBs titres at 36-42 months in our study. Previously, anti-HBs titres after primary immunization were reported as the strongest predictor of long term seroprotection [14]. We found that proportion of memory T-helper lymphocytes was correlated with longterm seroprotection which is similar to that reported by. Veiga, et al. [15]. A single double-strength booster dose of rHBV vaccine was also adequate in five children who lacked seroprotection despite primary immunization with atleast 3 rHBV vaccine doses.

The fact that all of the participants were receiving ART is a significant strength of our study. All patients in our ART clinic have meticulous records kept, and CD4 counts and other necessary laboratory parameters are routinely investigated and available for each patient. The limitations of our study include a small sample size and the difference in age of the study groups.

We conclude that a 3-dose double strength rHBV vaccination schedule offers comparable seroprotection to a 4-dose double strength rHBV vaccination schedule in

WHAT THIS STUDY ADDS?

- A 4-dose double-strength recombinant hepatitis B (rHBV) vaccination schedule for hepatitis B vaccination in children living with HIV (CLHIV) did not offer additional benefits in terms of higher seroprotection rates 36-42 months after primary immunization.
- A single double-strength rHBV vaccine booster dose was adequate in CLHIV who were found unprotected 36-48 months after primary immunization with atleast 3 doses of rHBV vaccine.

CLHIV receiving ART. Also, a single, double strength rHBV booster is adequate in children who were immunized previously with atleast 3 doses of rHBV vaccine.

Ethics clearance: Institutional Ethics Committee for Human Research of University College of Medical Sciences; No.: IECHR/2020/PG/68-R1 dated Dec 21, 2020.

Contributors: NY: data collection, analysis and interpretation, drafted the manuscript and revised it; PD: conceptualized the study, data analysis and interpretation, drafted the manuscript and provided critical inputs; SG: data interpretation, critical inputs in manuscript; BK, RG: laboratory methods, data collection and interpretation, provided critical inputs in the manuscript. All authors approved final manuscript and are accountable for the contents.

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SPECIAL ARTICLE

Single Parent Adoption: An Indian Perspective

PIYUSH GUPTA,[1] PAYAL GUPTA[2]

[1]Department of Pediatrics, University College of Medical Sciences, Delhi.
[2]Department of Ophthalmology, Fortis Hospital, Greater Noida, Uttar Pradesh.
Correspondence to: Dr. Piyush Gupta, Professor, Department of Pediatrics, University College of Medical Sciences, Delhi.
prof.piyush.gupta@gmail.com

Adoption is gaining an increasing acceptance in the society, and is also being researched well globally; yet, the concept of single parent adoption (SPA) is viewed with scepticism. Although, it is legally possible for prospective parents to proceed with adoption, there are several barriers which have made SPA a lengthy and arduous process. We present a strong case for SPA, in the absence of adequate research, by citing a basic flaw when fighting for SPA. Comparing SPA with a "two-parent model" is not only unreasonable but also unfair as it deprives a single parent of the pleasures of parenting and also denies the child an opportunity of living in a home outside the confines of an orphanage.

Keywords: CARA, Child, Juvenile Justice Act, Rights.

Single Parent Adoption (SPA) defies the basic structure of a family, wherein a child is reared by a couple, namely a father and a mother [1]. The non-traditional concept of a family with a single mother, a single father, or a homosexual couple is still often looked down or frowned upon by certain echelons of society. Individuals who are not a part of a heterosexual, monogamous, and procreative marriage are not considered suitable candidates for parenting and face discrimination in various forms.

Adoption is increasingly and seemingly widely being accepted and researched in India, but SPA is still a grey area with limited scientific work and an uncertain air. Although, it is legally possible for prospective single parents to proceed with adoption, there are several constraints with respect to age (both, of adopter and adoptee), gender, and religion. The Ministry of Women and Child Development, Government of India (MWCD, GOI) in conjunction with Juvenile Justice Act (Care and Protection of Children), 2015 (JJ Act 2015) has laid down a list of criteria for adoption [2]. Central Adoption Resource Authority (CARA) is the nodal body under MWCD, GOI which deals with and monitors adoptions in India. The JJ Act allows for single parents to adopt children, but there are many hurdles that they must overcome to do so. Single parents are often required to provide additional documentation and undergo extra scrutiny during the adoption process. This can be time-consuming and expensive that may deter many prospective parents from pursuing adoption. Despite these strict guidelines and a laborious process of adoption, there has been a steady increase in SPA in the recent past in our country [3]. There being a paucity of published literature on SPA in India, a couple of themes are common to what little research has been done globally. The adjustment issues in terms of adoption success, educational achieve-ments, emotional and behavioral stability, and dealing with identity crises, have been found to be similar in adoptees of single versus two parent adoptions [4,5]. A few studies have even reported lower emotional and behavioral issues in adoptees of SPA, indicating that an SPA setup might be better suited to emotionally disturbed children [6].

The desire to be a parent in a single woman or man is no different than that of a couple. On the other side, the motivation is rather stronger and more grounded. The struggles of adoption, though differently angled in both genders, are equally challenging. DeJean, et al. [7] have demonstrated the society's prejudiced opinion based on the parent's gender. While they believe that men are motivated, responsible, financially stable, and thus better suited for the role of single father; single mothers supposedly have less intelligence, resources, security, and sense of duty needed for independent child rearing. However, irrespective of the gender of the single parent, the psychological and educational outcomes of children have been found to be comparable [8].

More often than not, the most robust theories are derived from best-practices, scientific research, or from plain old common sense. In the absence of the former, we must look to the latter. And the decision to ease SPA in India must be made now keeping the best interest of the child in perspective, for we are stuck in a peculiar logjam as shown in **Fig. 1**. In a manner of speaking, we are stuck in a vicious loop, which, at first glance, appears unbreachable. Who takes the first step?

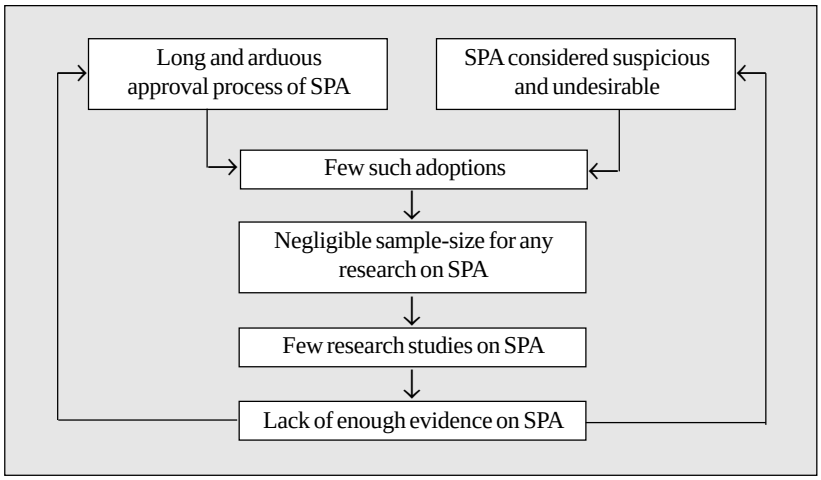

Fig. 1 The lack of evidence in single parent adoption (SPA).

If researchers really do not have overwhelming evidence supporting SPA, do we simply ease the approval process for single parents in the hope that it gives us a bigger sample size for the next set of longitudinal research? Would it not be cavalier to do so? To make a policy decision that risks the lives of children on the basis of a "let's-see-what-happens" attitude.

However, there is a basic flaw in this premise, something that makes us realize that the vicious loop is of our own making and has no real basis for every research in the subject, the handful of studies that have been conducted, compares SPA to two-parent adoption. The only scenario in which this makes sense, is if the number of adoption requests is higher than the number of children languishing in orphanages. Only then does two-parent adoption become the alternative for SPA. It is; however, not the case. There are fewer requests for adoption being made than the number of children in need of a home. So, the alternative to a single parent is no parent. When a single parent is denied adoption due to a process biased against them, the child in question is most likely to remain in an orphanage rather than be adopted by two parents.

Thus, every research, study, anecdote being analyzed, from here on, must compare the life of a child in single-parent household with the life of a child in an orphanage. It is easy to fathom that a child's life with substantial financial and emotional support from a single parent far outstrips his/her chances in a one-size-fits-all orphanage run by either the governments- or some non-governmental organization (NGO). It is the need of the hour to abolish any policy that discriminates against SPA, while keeping the best interests of the child in mind. What will surely follow is a rise in number of children finding homes with single parents, increasing our ability to do research and understanding the nuances of the subject. And simultaneously, the children find homes that offer better care than an orphanage.

Simply put, a policy based on evidence-based research is always preferred. But in its absence, some common sense is not a bad recourse, either.

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Nutritional Supplementation to Prevent Infection in Household Contacts of Tuberculosis Patients

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SUMMARY

This was a field-based, open-label, cluster-randomized controlled trial, in which household contacts of 2800 patients with microbiologically confirmed pulmonary tuberculosis across 28 tuberculosis units of the National Tuberculosis Elimination Programme across four districts of Jharkhand, India, were enrolled. The tuberculosis units were randomly allocated 1:1 by block randomization to the control group or the intervention group. Although microbiologically confirmed pulmonary tuberculosis patients in both groups received food rations (1200 kcal, 52 grams of protein per day with micronutrients) for 6 months, only household contacts in the intervention group received monthly food rations and micronutrients (750 kcal, 23 grams of protein per day with micronutrients). After screening all household contacts for co-prevalent tuberculosis at baseline, all participants were followed-up actively, for the primary outcome of incident tuberculosis (all forms). There were 10,345 household contacts, of whom 5328 (94·8%) of 5621 household contacts in the intervention group and 4283 (90·7%) of 4724 household contacts in the control group completed the primary outcome assessment. The authors detected 31 (0·3%) of 10,345 household contact patients with co-prevalent tuberculosis disease in both groups at baseline and 218 (2·1%) people were diagnosed with incident tuberculosis (all forms) over 21,869 person-years of follow-up, with 122 of 218 incident cases in the control group [2·6% (122 of 4712 contacts at risk), 95% CI 2·2-3·1; incidence rate 1·27 per 100 person-years] and 96 incident cases in the intervention group [1·7% (96 of 5602), 1·4-2·1; 0·78 per 100 person-years], of whom 152 (69·7%) of 218 were patients with microbiologically confirmed pulmonary tuberculosis. Tuberculosis incidence (all forms) in the intervention group had an adjusted IRR of 0·61 [95% CI 0·43-0·85; aHR 0·59 (0·42-0·83)], with an even greater decline in incidence of microbiologically confirmed pulmonary tuberculosis [0·52 (0·35-0·79); 0·51 (0·34-0·78)]. This translates into a relative reduction of tuberculosis incidence of 39% (all forms) to 48% (microbiologically confirmed pulmonary tuberculosis) in the intervention group. An estimated 30 households (111 household contacts) would need to be provided nutritional supplementation to prevent one incident tuberculosis. The authors conclude that nutritional intervention was associated with substantial (39-48%) reduction in tuberculosis incidence in the household during the two years of follow-up.

CRITICAL APPRAISAL

Evidence-Based Medicine Viewpoint

This cluster-randomized controlled trial (RCT) [1] examined the impact of nutritional supplementation provided to household contacts of adults with pulmonary tuberculosis, on the incidence of tuberculosis disease in them. The elements of the research question can be broken down to: Population/Problem (P): Household contacts of adults with microbiologically confirmed pulmonary tuberculosis; Intervention (I): Nutritional supplementation for 6 months; Comparison (C): No nutritional supplementation; Outcomes (O): Incidence of all types of tuberculosis; Timeframe of outcome measurement (T): Two years; and Setting (S): Community setting among people living in 'tuberculosis units.' The unit of randomization was the tuberculosis unit (and not individual participants) in four districts of Jharkhand.

The participants eligible for inclusion were household contacts of any adult with microbiologically confirmed pulmonary tuberculosis (index case) as per the criteria in the National Tuberculosis Elimination Programme (NTEP). A 'household contact' was defined as those living in the same house, consuming food from the same kitchen for any length of time, and not already receiving tuberculosis therapy. There were no other exclusion criteria specified by the authors.

The sample size was meticulously calculated, taking into consideration the population incidence of pulmonary TB, number of index cases within a tuberculosis unit, incidence of TB among household contacts, estimated decline in TB with the intervention, design effect, average family size in the

target population, and the usual alpha error. The calculation suggested that a sample size of 11200 household contacts randomized into two arms would have at least 80% power to detect a 50% decline in the incidence of TB with the intervention.

The intervention was daily 'nutritional supplementation' amounting to 750 kcal, 23 g protein, & one recommended dietary allowance (RDA) of micronutrients, per household contact. Those <10y old received half of this. It was administered as a monthly ration that could be either home-delivered, or collected from specific locations. The comparison group of participants did not receive these rations. However, the index case in both groups received daily nutritional supplements amounting to 1200 kcal, 52g protein, and one RDA of micronutrients. Household contacts received supplementation throughout the duration of treatment of the index case (viz 6 months for drug sensitive TB, and 12 months for drug resistant TB). However, supplementation could be extended for up to 12 additional months in adult contacts with BMI <16 kg/m^2, adolescents with BMI Z score <2, and younger children with weight-for-age Z score <2. Apart from the intervention, both groups were treated similarly.

The primary outcome was development of TB (any type) among the household contacts. Other outcomes were pulmonary TB, other TB, other acute infections (notably malaria, diarrhea, lower respiratory tract infection, hospitalization for fever), change in weight among contacts, and mortality with acute fever during the intervention period. Cost of the intervention (including delivery and implementation) was calculated.

The intended follow-up period was 2 years, with monthly visits during the first year, and 3-monthly thereafter (i.e., total 16 follow-up time points). However, due to COVID exigencies, the protocol was modified, extending the follow-up period to a common closing period. Therefore, some participants could be followed-up for longer than 2 years; whereas almost one-fifth could be followed up for only 18 months. Each contact was followed-up until they developed TB, or their data were censored.

The main results among household contacts are summarized in **Box I**.

Critical appraisal of the RCT

Critical appraisal using the current Cochrane Risk of Bias (RoB) II tool for cluster RCTs [2] is summarized in **Table I**. There was low RoB in three domains, and some concerns in two domains. Considering the criteria in the GRADE-ing of evidence [3], this trial would qualify for downgrading by at the most one point for the issues highlight in the RoB assessment. There is no significant imprecision, or indirectness noted. Thus the trial can be considered to contribute moderate to high quality evidence.

The trial had numerous methodological refinements raising confidence in the reported findings. The state of Jharkhand was chosen for specific reasons that are described well. The selected districts were not chosen randomly, but were apparently based on the case load and logistic feasibility of implementing the intervention. The trial was aligned with the prevalent NTEP system and procedures, facilitating applicability of the findings. A local non-Governmental organization was involved in data collection of serious adverse events and deaths. A Data Safety and Management Board was established for the trial, although there was no interim analysis. The trial investigators incorporated multiple logistic refinements to ensure appropriate delivery of nutritional supplementation, and also attempted to ensure appropriate consumption. There are no grave ethical concerns in the trial design or implementation.

Additional refinements included the use of clear definitions for terms such as index case, household contact, tuberculosis unit, duration of intervention, incident TB, co-prevalent TB, lost to follow-up, etc. At enrolment and during the trial, the index cases were counselled regarding consuming a balanced diet, adhering to therapy, and cough hygiene. Meticulous attempts were made to ensure appropriate follow-up and track those who were unavailable.

Despite these refinements, some aspects are unclear. For example, the basis for choosing to supplement diet with specifically 750 kcal and 23g protein is unclear. Similarly, the rationale for providing exactly half of this to all children <10 y old (irrespective of age) is also unclear.

The age-wise analysis of incident TB among contacts confirms that the beneficial effect of nutritional supplementation was driven by reduction in TB only in adults. There was no such benefit among young children <5y or

Box I Main Results Among Household Contacts in the Study

TB (any type)

96/5602 vs 122/4712 equivalent to 1.7% (CI 1.4, 2.1) vs 2.6% (CI 2.2, 3.1)[a]

Incidence rate of TB (per 100 person-years)

0.78 (CI 0.64, 0.96) vs 1.27 (CI 1.00, 1.61)[a]

Incidence rate of microbiologically confirmed TB (per 100 person-years):

0.51 (CI 0.38, 0.68) vs 0.95 (CI 0.73, 1.24)[a]

Incidence rate of clinically diagnosed TB (per 100 person-years):

0.28 (CI 0.18, 0.44) vs 0.30 (0.19, 0.56)

Incidence of other acute infections, and deaths due to febrile illness, was apparently similar in the two groups.

[a]$P<0.05$

Table I Critical Appraisal of the Trial Using the Current Cochrane Risk of Bias (RoB) II Tool for Cluster Randomized Controlled Trials

Domain and Comments	*Assessment*
RoB arising from the randomization process	
• The allocation sequence (for tuberculosis units) was generated by a remotely located statistician using computer generated random numbers.	*Low RoB*
• Block randomization was used, however block size(s) is/was not specified.	
• The allocation ratio was 1:1. Although tuberculosis units (and not individuals) were randomized, the data of individuals were reported.	
• Allocation was concealed from the investigators, although it is unclear how this was done, and also whether it remained concealed until the clusters were assigned to the intervention. However, it is unlikely that participants could have self-selected themselves to either trial arm.	
• Baseline characteristics viz. age distribution, gender distribution, caste status, occupational background, access to the pubic distribution system, personal habits (tobacco use, alcohol consumption), economic status, and proportion of children receiving prophylaxis; were comparable suggesting adequacy of the randomization process.	
• However, there a statistically significant difference in the baseline prevalence of undernutrition among adults (38.3% vs 34.9%) and children, although this was not shown in the Table of baseline characteristics.	
• Although trial participants were neither identified not recruited before the clusters were randomized, it may not create bias in this study. It is also unlikely that participant selection was affected by knowledge of the intervention assigned to the cluster.	
RoB due to deviations from the intended interventions	*Low RoB*
• Participants were aware that they were in a trial; however the nature of the intervention was such that participants could not be blinded to their allocation.	
• Similarly, the trial personnel also were aware of the allocation of individual clusters (and thereby households). These personnel were responsible for periodic symptom screening of contacts (to direct them towards diagnostic tests).	
• There were no apparent deviations from the assigned intervention.	
• It is unclear whether knowledge of the assigned interventions could have altered the behavior of participants (as no calculations of their caloric or protein intake during the intervention period, and thereafter, were made). Adults in both trial arms gained weight during the intervention period (suggesting a potential for behavioral alteration), although the intervention group showed a statistically significant greater weight gain. Further, the limited number of children in both groups had comparable weight gain, reiterating the same concept.	
• If there were deviations from the intended allocation (i.e. participants in the comparison group consumed additional nutrition on their own), it would have resulted in a narrower (if not nil) difference between the trial arms. Since there was still a statistically significant difference, it suggests a robust result.	
RoB due to missing outcome data	*Some concerns*
• It is unclear whether data from all the clusters randomized were available for analysis, as the authors reported data by participants rather than clusters.	
• After randomization, there were 5621 participants in the intervention group, and 4724 in the comparison group. Data for the primary outcome were available in 5328 (94.8%) and 4283 (90.7% respectively).	
• Data were missing in the remainder due to withdrawal, co-prevalent TB, deaths during the intervention period (all three were comparable between groups) and loss to follow-up. However, there was almost 2.5 times greater loss to follow-up in the comparison group (3.0% vs 7.4%). The reasons and impact of this are unclear. It is reasonable to wonder whether the missing data could have altered the estimate of benefit of the intervention (if they had unfavorable outcome). Although the authors stated that an intention-to-treat (ITT) analysis was performed considering those with missing data, it is unclear how this was done.	
• When the study was terminated, there were 167 (3.0%) and 349 (7.4%) participants respectively, whose follow-up data were unavailable.	
RoB in measurement of the outcome	*Some concerns*
• The method of measuring the outcome was appropriate, and there does not appear to be any inter-group difference in the method of ascertaining the outcome.	
• Those recording the primary outcome were independent of the trial personnel, however it is unclear if they were blinded to the intervention. It is also unclear whether they were aware that a trial was in progress.	

- As TB was diagnosed clinically in over 25% household contacts, knowledge of the allocation could have influenced the outcome.

RoB in in selection of the reported result *Low RoB*

- The outcomes reported were decided a priori.
- Additional post hoc analyses included splitting TB cases as 'microbiologically confirmed' and clinically diagnosed. However, given that this is permissible under the NTEP, it is acceptable.
- None of the other outcomes appear to have been selected for reporting, based on the result.

older children 6-17y. This is disappointing from the perspective of pediatricians. Further, even among adults, the benefit was observed only among males, and especially those who were not undernourished at baseline.

One of the major challenges in this study is the possibility of food sharing within a household. Given that only index cases in the comparison group received supplementation, it is possible (even probable) that some of it may have been shared with family members. This is indicated by the nearly 2% weight gain over 6 months amongst adult household members, irrespective of gender. This gain which was about half of that recorded amongst adults in the intervention group, needs explanation. Further, the overall prevalence of poor nutrition (defined by low BMI) declined more in the comparison than the intervention group.

Similarly, children between 6 to 17y (male and female) in the comparison group gained about 6.5% weight over 6 months. Although this could be simply due to natural growth among children, the possibility of food sharing cannot be ruled out, especially as the gain was only 2% lower than in those receiving the intervention. Given these concerns, it would have been logical for the authors to report the weight gain in the index cases. If there was no food sharing, the gains would have been similar in both groups. Of course, additional analysis of inter-group weight gain patterns by the number of household contacts would have thrown further light on this issue. Unfortunately, these data were not reported.

Children <5y (both boys and girls) showed almost 20% weight gain over 6 months, and surprisingly the gain was similar amongst those in the intervention as well as comparison groups. The comparable weight gain in both groups raises several questions viz., *i*) Could it be because young children in the comparison group also received some supplementation, either through food sharing or behavior change within families? *ii*) Could it be because young children in the intervention group were deprived of the nutritional supplementation allocated to them, because of diversion to others in the household? *iii*) Had increase in weight *z* scores been reported instead of absolute weight gain, it would have been feasible to interpret whether the gain was due to natural growth (in which case *z* scores would remain unchanged) or nutritional supplementation (*z* scores would increase). Unfortunately this was not reported.

In this trial, incident TB among household contacts was determined by screening for symptoms to make a presumptive diagnosis of TB, followed by referral to a health facility for clinical examination and sputum evaluation. Sputum was examined by microscopy or nucleic acid amplification. Thus it is unclear how symptomatic contacts who did not produce sputum were evaluated. Although the NTEP may not have a provision for such situations, this would be expected in a well-designed and conducted trial. The issue is particularly relevant to young children, wherein sputum is not usually available, and multiple gastric aspirate/lavage specimens are required for diagnosis.

There are several interesting findings reported in the publication [1] but not sufficiently highlighted or explored. For example, among children younger than 5 years, incident TB was over three times more frequent amongst those who received nutritional supplementation (8.3% vs 2.5%) despite them being 1.5 times more likely to have received INH prophylaxis. This unusual situation is of great interest to pediatricians and public health specialists, and warrants further exploration.

Despite the well-established National guideline [4] recommending INH prophylaxis for children <6y in contact with adult pulmonary TB (prevalent during the trial period), it appears that only 1 in 6 such children actually received it. This indicates a gap between programmatic policy vs practice. The broader implication is that if nutritional supplementation were to be initiated at the programmatic level, there is risk of similar gaps in practice once the stringent project related oversight is replaced by routine implementation.

It is important to note that current guidelines recommend INH preventive therapy to contacts across all age groups [5]. This raises two subsidiary questions: *i*) If the programmatic implementation of this remains similar to that among children, little may be achieved by it; and *ii*) On the other hand, if it is implemented in a robust manner, would there be need of nutritional supplementation to prevent the development of TB?

Although the trial overall showed lower incidence of TB among contacts receiving nutritional supplementation, this appears to be restricted to those with microbiologically confirmed TB. Among those with clinically diagnosed TB, there was no inter-group difference among adults, whereas it was actually almost three times higher among children (<18y). This unusual observation has not been explored.

It is interesting that although females outnumbered males amongst household contacts (11:9 ratio), the reverse was true for those who developed incident TB, with approximately 55% cases being male. The median time for the development of TB among contacts was almost 17 months. In fact, almost a fourth of the cases among contacts were diagnosed beyond 2 years of follow-up. This suggests a few interesting possibilities. If the contacts were being infected by the index case, it should have occurred during the peak of infectivity viz., within the first few weeks after starting treatment of the index case. Therefore confirmatory diagnosis after several months, and that too almost a year after the index case stopped therapy, suggests slow progression from infection to disease. The alternate explanation that contacts were getting infected from some other source is even less plausible. This also raises the question of how long the contacts of successfully treated cases should be followed up, to be confident that they do not develop TB.

There were 31 contacts who had co-prevalent TB (i.e., TB was detected even before the intervention was implemented). This means that their family members were exposed to two index cases. It would have been interesting (and relevant) to record the incidence of TB in such families.

What could be the mechanism whereby nutritional supplementation for 6 months, prevented the development of TB for over 2 years? Could it be that short-term enhanced nutrition somehow altered the immune status, resulting in long-term protection? As there was no reduction in the incidence of other infections, if 'immunity' were responsible, could it be restricted to cell-mediated immunity? Would the 'immunity' wane over time? Although nutritional supplementation of contacts was done for six months (in the majority), the benefit of reduction in TB became apparent only after 9 months, i.e. well after cessation of the intervention. If nutrition-facilitated, enhanced cell-mediated immune function, is it acquired slowly? Pathophysiologic studies may be required to address these questions.

It is encouraging that there did not appear to be any drug resistant TB among 2800 adults. This is useful information from the public health perspective.

It appears that the monthly cost of nutritional supplementation per adult contact was about Rs 338/- (1USD = 71.17 INR on the project start date) [6] or approximately Rs 11/- per day. This remarkably low cost included delivery costs as well. However, the monthly cost of providing less than double the supplementation, to index cases was almost thrice the cost i.e.. Rs 925/-, or Rs 30/- per day.

Conclusion: This methodologically robust, low risk-of-bias randomized trial suggests that nutritional supplementation offered to household contacts of adult TB cases, could reduce the incidence of TB among adult family members, although there may not be any impact on children. The issues highlighted above suggest although the intervention appears promising, there are several challenges to be overcome for successful implementation a s a public health strategy.

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JOSEPH L MATHEW
Department of Pediatrics, PGI,Chandigarh.
drjoseph.l.mathew@gmail.com

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Pediatric Tuberculosis Specialist's Viewpoint

Among all the risk factors that accelerate tuberculosis infection, undernutrition tops the list, especially in childhood tuberculosis. The World Health Organization (WHO) recommends integration of childhood tuberculosis preventive and diagnostic services with community nutritional services to address tuberculosis and undernutrition syndemic [1]. In the study under discussion [2], children aged below 17 years constituted 40% of cohort in this controlled study of nutritional supplementation of household contacts (HHCs)

of microbiologically confirmed pulmonary tuberculosis. Children younger than five years, who are known to have the highest risk of tuberculosis infection and disease progression, formed 11% of the study population.

The authors have shown an overall reduction of incidence of tuberculosis by 39% in the nutritional supplementation group compared to the control group (0.78 vs 1.27) [2]. However, paradoxically, incident tuberculosis cases were higher in intervention group compared to control group in children < 5 years, who are the most vulnerable HHCs (0.58 vs 0.27). There was no disparity either in nutritional status or tuberculosis preventive therapy (TPT) between the groups. What can explain this?

Surprisingly, authors have not discussed this paradoxical finding. There was only a modest reduction of incident rate in children of ages 6-17 years (0.38 vs 0.53). This calls for deeper look into the strategy to find out the factors responsible for the same. What is worrisome for pediatricians is, only 16% of children younger than five years exposed to confirmed pulmonary tuberculosis were initiated on TPT, which is an essential strategy to prevent pediatric tuberculosis. This could have confounded the results in them. Hence, along with nutritional intervention, other strategies like TPT, and early detection and treatment of adult tuberculosis, have to be strengthened to achieve the goal.

Despite these limitations in children, overall reduction in incident tuberculosis and further reduction in microbiologically, confirmed pulmonary TB in adults by nutritional supple-mentation will have indirect impact on control of pediatric tuberculosis.

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CK INDUMATHI
Department of Paediatrics,
St John's Medical College Hospital, Bengaluru,
ckindumathi@gmail.com

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Public Health Specialist's Viewpoint

Tuberculosis remains one of the most significant public health problems in India, with more than 3 million people affected annually, about 1.3 million out of them estimated to be children [1]. Despite it being such a significant problem in India and in other low- and middle-income countries (LMICs), there have been limited advances in its prevention, diagnosis or treatment.

Most high-income countries controlled tuberculosis without a vaccine or treatment, primarily by equitable improvements in nutrition, living and working conditions of its citizens. National Tuberculosis Elimination Program (NTEP) commits to eliminate tuberculosis by the year 2025, relying predominantly on a treatment-based approach to control and eliminate the disease.

This rigorously conducted study [2] provides evidence of effectiveness of nutrition supplementation of household contacts. At 39% reduction of all forms of tuberculosis incidence among households, it promises to be one of the most effective public health interventions to control the disease. In the absence of an effective vaccine, strong evidence of its effectiveness, and low costs in administering (<5 USD per household contact), there is a compelling reason to integrate this strategy within NTEP. Given the syndemic of tuberculosis and malnutrition, there is also a critical need for focused multi-sectoral efforts to enhance availability of nutritious food in food scarce regions of India, such as where this study was conducted.

Since the diagnosis of tuberculosis in NTEP relies heavily on sputum examination, there is an inadequate identification of tuberculosis among children, who often swallow their sputum. It is estimated that there are closer to 1.5 lakh cases of childhood tuberculosis annually, that are not reported within NTEP. In this study, which relied on the existing program mechanisms of detecting tuberculosis, very few children younger than five years (n=11) were found to have tuberculosis during a 2-year follow-up. This underscores the urgent need for diagnostic tools, simplified algorithms, and training of program staff for detection of childhood tuberculosis.

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PAVITRA MOHAN
Basic Health Care Services, Udaipur, Rajasthan.
pavitra@bhs.org.in

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Vaccination of Pediatric Patients With Autoimmune Inflammatory Rheumatic Diseases – EULAR/PRES Updated Recommendations, 2021

POTHIREDDY SHARANYA,[1] VAISHNAVI RANI KOTA[2]

[1]Department of Pediatrics, Maulana Azad Medical College (University of Delhi), 2, BSZ Marg, Delhi 110002.
[2]Department of Pediatrics, Vishwabharathi Medical College (YSR University of Health Sciences), Kurnool 518467, Andhra Pradesh.
Correspondence: Dr. Vaishnavi Rani Kota, Viswabharathi Medical College and General Hospital, RT Nagar, Penchikalapadu, Kurnool, 518467, Andhra Pradesh. vaishnavikota853@gmail.com

The recommendations for vaccination in pediatric autoimmune and inflammatory diseases were initially given by European Alliance of Associations for Rheumatology (EULAR) in the year 2011. In the past decade, recommendations were updated for adults in 2019. EULAR/ Pediatric Rheumatology European Society (PRES) has now published the updated recommendations based on the increased level of evidence on safety, efficacy and immunogenicity of vaccines. We, herein, update the readers about the new changes in the recommendations, and emphasize the changes compared to 2011 recommendations to make it readily accessible for the specialist to guide families of children with autoimmune inflammatory disorders.

Keywords: *Guidelines, Immunization, Juvenile idiopathic arthritis, Systemic lupus erythematosus.*

Juvenile idiopathic arthritis is the most common rheumatic disorder in children with incidence of 0.8-22.6 per 1 lakh children. Other autoimmunity and auto-immune disorders have been showing an increasing trend over the past decade, and so are the associated complications. The vaccination coverage in children with juvenile idiopathic arthritis is very low. The immunization coverage in other pediatric patients with autoimmune/inflammatory diseases (PedAIIRD) is not known. PedAIIRD have increased risk of infections due to the immunomodulatory, and immuno-suppressive drugs as well as due to the disease activity per se [1,2]. Vaccination in these children is of utmost importance to prevent the diseases and their complications. However, certain vaccines are contraindicated in these children and booster doses may be required for certain other vaccines.

NEED FOR THE UPDATE

In the current era of treatment for the autoimmune diseases, the biological disease-modifying antirheumatic drugs (bDMARDs) include Tumour Necrosis Factor inhibitors i.e., etanercept, infliximab, anti-IL 1 i.e., anakinra, anti-IL 6 i.e., tocilizumab, and B cell depletors like rituximab are being increasingly used. Currently, EULAR/PRES published the updated set of recommendations in 2022 [3]. The first EULAR recommendations were formulated in 2011, which was based mainly on adult studies [4]. The 2011 guidelines consist of 15 recommendations. In the past decade the efficacy, immuno-genicity and safety of vaccines in relation to treatment with DMARDS had been well studied. The main focus of the update of EULAR 2022 was on the effect of glucocorticoids and biological DMARDs on the vaccines.

The patients are considered immunosuppressed, when they receive steroids and conventional synthetic (cs) DMARDs at dosages provided in **Table I**. All patients receiving bDMARDs or tsDMARDs or their combination irrespective of the dosage are considered immuno-suppressed. DMARDs can be divided into three types: Conventional synthetic, Biological, Targeted synthetic i.e., Janus kinase inhibitors. Risk of serious infections is high in patients treated with standard dose or high dose biological DMARDs compared to conventional DMARDs. The risk was lower in patients on methotrexate [2]. The immune system gets compromised due to DMARDs therapy, which can lead to impaired immune response to vaccine by altering the T cell and B cell response.

Table I Immunosuppressant Drugs and Dosages for Immuno-suppression

Drug	*Dosage*
Prednisolone	≥0.5 mg/kg/d for ≥2 wk
Cyclosporine	>2.5 mg/kg/d
Azathioprine	≥3 mg/kg/d
Cyclophosphamide (oral)	>2 mg/kg/d
Leflunomide	≥0.5 mg/kg/d
Mycophenolate mofetil	≥30 mg/kg/d or >1000 mg/d
Methotrexate	≥15 mg/m2/wk or ≥25 mg/wk
Tacrolimus	>1.5 mg/d

Adapted from Jansen, et al. [3].

OVERARCHING PRINCIPLES

The treating specialist should assess the vaccination status of the child yearly and accordingly recommend the necessary vaccines in addition to the National Immunization schedule, and withhold certain vaccines based on disease severity and treatment status. The immunization coverage is low in pedAIIRD, and it is the responsibility of the treating specialist to appropriately counsel the parents regarding risk of infections, vaccine preventable infections and adverse effects. Yearly assessment of the disease severity and treatment status is recommended, and a shared decision making to be considered [1,3].

Vaccines are to be administered in the quiescent stage preferably. There are not enough pediatric studies to indicate lower vaccine safety, immunogenicity or efficacy during high or low disease activity states. There is conflicting evidence regarding this in adults [5,6]. Therefore, it would be better if the child is vaccinated during quiescent phase but there is no contraindication to accinate during high disease activity stages.

Vaccination should be given 2 to 4 weeks prior to the starting of the immunosuppressive therapy, if possible (especially B cell depleting therapies), but the treatment should not be withheld or postponed. Methotrexate in children is not associated with decreased antibody levels whereas in adults reduced seroprotection was found. Regarding bDMARDS, especially B cell depleting agents like rituximab, patients showed absent to reduced humoral immune response until 6 months of stoppage of treatment [7]. TNF inhibitors and anti-IL6 agents did not impair any seroprotection. IVIG is associated with lower seroprotection and antibody response within 9 months of administration [8]. Therefore the vaccination must be planned before therapy, if possible, or immune response should be measured after vaccination and boosters to be given based on the response.

Adherence to the National immunization schedule for general and travel vaccinations as well except for live attenuated vaccines in immunosuppressed patients. This emphasizes the improved overall vaccination coverage in the patients as the coverage in children with autoimmune disorders is very low. All the non live vaccines can be given as there are no adverse events on administration of these vaccines and seroprotection rates are also comparable to healthy controls, except those patients on high dose glucocorticoids and B cell depleting agents.[7]

In pediatric AIIRD on DMARD and glucocorticoid therapy, non-live vaccines can be administered without any contraindication. The vaccines produced no adverse effects or aggravate the disease process, the immunogenicity was comparable in patients using DMARDs or glucocorticoids. But the the humoral immune response may be hampered in children receiving the bDMARDs and high dose glucocorticoids [7,2].

Except for MMR booster and varicella vaccines, other live attenuated vaccines are avoided in pediatric AIIRD patients. Because of the risk of infection due to the attenuated live pathogen, live vaccines are contraindicated except for MMR and varicella [9,13].

RECOMMENDATIONS

Non-Live Vaccines

Influenza vaccine: Non live seasonal influenza vaccine is highly recommended for pedAIIRD on immunosuppressive therapies. Large number of adult studies showed increased risk of complications and mortality due to influenza in AIIRD patients on immunosuppressive drugs. Based on the available studies; the safety, efficacy and immunogenicity in pedAIIRD who were on low dose steroids, bDMARDs and with low disease activity was comparable to healthy individuals except for the children on high dose glucocorticoids, TNFi and those with high disease activity [5,6,10]. The efficacy of the vaccine was good, as extrapolated from adult studies; though, pediatric studies were lacking.

Pneumococcal vaccine: It is recommended in all non-vaccinated pedAIIRD children. PCV 10 or PCV 13 is recommended as per NIS. The safety and efficacy was comparable to healthy subjects. PPSV 23 booster administration in adults showed decreased invasive pneumococcal disease but there is paucity of pediatric literature. However PPSV 23 can be given in immunosuppressed children and children with SLE once every 5 years in accordance with adult guidelines [5]. PPSV23 is avoided in children with cryopyrin associated periodic syndrome (CAPS) as per the taskforce.

Tetanus vaccine: It is to be administered as per NIS and as per recommendations in general populations. Passive immunization is recommended in children receiving B cell depleting therapies in the past 6 months if there is indication for TT vaccination. In children receiving B cell depleting therapy the humoral immune response is severely hampered until 6 months, therefore passive immunization is necessary if TT vaccination is indicated [11].

HPV vaccine: HPV vaccination is strongly recommendation for jSLE children who are not vaccinated. SLE patients have high risk of persistent HPV infection and high risk of squamous intraepithelial lesions and cervical cancer. The vaccine is effective in preventing cervical intraepithelial neoplasia caused by HPV16/18. Adult studies showed that HPV vaccine is highly immunogenic in SLE patients, therefore it is strongly recommended in children as well [12].

Table II Recommendations as per EULAR 2021 Updated Guidelines and Changes From 2011

Recommendations	*Changes to 2011*
Non-live seasonal influenza vaccination should be strongly considered for paediatric patients with AIIRD treated with glucocorticosteroids or DMARDs	'Strongly' has been added to this recommendation.
Pneumococcal vaccination with PCV10 or PCV13 is recommended in all non-vaccinated paediatric patients with AIIRD.	PCV 10/13 is now 'recommended' instead of 'should be considered' in all non-vaccinated pedAIIRD patient.
Tetanus vaccination should be administered in accordance with recommendations for the general population. In case of an indication for tetanus toxoid vaccination, passive immunisation is recommended for patients receiving B-cell depleting therapy in the past 6 months.	Recommendation on B-cell depleting therapy is new.
Human papilloma virus vaccination should be strongly considered in non-vaccinated JSLE patients	'Should be advised' has been replaced for 'should be strongly considered.'
MMR booster vaccination can be administered to patients on MTX; and, can be considered in patients treated with low-dose glucocorticoids TNFi, anti-IL1 and anti-IL6 therapy.	MMR boosters vaccination can be 'administered' instead of 'considered' in patients on MTX. TNFi, anti-IL1 and anti-IL6 therapy has been added to this recommendation.
VZV vaccination should be strongly considered in varicella vaccination/infection naive patients on MTX; and, can be considered in varicella vaccination/ infection naïve patients on low-dose glucocorticosteroids, TNFi, anti-IL1 and anti-IL6 therapy.	This recommendation is now specified per treatment. In patients on MTX, 'strongly' is added to the recommendation. Therapies have been specified in which VZV vaccination can be considered .
Yellow fever vaccination should be avoided in all immunosuppressed patients.	This recommendation has been changed in 'avoid in all immunosuppressed patients' instead of 'can be considered in patients on MTX.

Adapted from Jansen, et al. [3]. AIIRD: autoimmune/inflammatory rheumatic disease; DMARD: disease-modifying anti-rheumatic drug; IL: interleukin; jSLE: juvenile systemic lupus erythematosus; MMR: mumps measles rubella; MTX: methotrexate; PCV: pneumococcal conjugate vaccine; TNFi: tumour necrosis factor inhibitor; VZV: varicella zoster virus.

Live-Attenuated Vaccines

Measles-mumps-rubella: The MMR booster dose of vaccination can be given to children on MTX therapy and can be considered in children treated with low dose glucocorticoids, TNFi, anti-IL 1, anti-IL 6 therapy. No adverse effects were noted after giving MMR to patients on MTX and no vaccine induced infections were noted [13]. However, persistence of the antibodies may be shorter in pediatric population. In children receiving low dose corticosteroids, TNFi, anti-IL 1, anti-IL 6 therapy no adverse effects were observed after receiving vaccines, but the level of evidence is low for a definitive statement [13].

Varicella Zoster virus vaccines: This vaccine is to be strongly considered in patients on MTX therapy who are infection naïve and it can considered in patients on low dose glucocorticoids, TNFi, anti-IL1, anti-IL 6 therapy. In immunocompromised patients the risk of complications is very high and can lead to severe herpes zoster [13]. Therefore, patients on MTX monotherapy are recommended for VZV vaccination as no serious adverse effects were seen except for mild rash which was treated by acyclovir [3,13]. Patients on low dose glucocorticoids, TNFi, anti-IL 1, anti-IL 6 therapy the vaccine can be considered by weighing the risk of infection and vaccine induced infection.

Yellow fever vaccine: This is to be avoided in all immunosuppressed children. There is no data regarding the safety of vaccine in pedAIIRD patients. If the vaccine is to be considered, then the treatment is to be interrupted, according to the guidelines [14].

To summarize, the current update, the guidelines laid emphasis on the safety profile of the vaccines and to improve the overall coverage in the studies. Many of the guidelines were formulated based on the adult studies taking paucity in pediatric data into consideration. High dose glucocorticoids and B cell depleting agents have found to hamper the humoral response to vaccines. Vaccines recieved on MTX therapy were found to have comparable antibody levels to healthy controls. Seroprotection was achieved when vaccine was received on treatment with TNFi but the level of antibodies rapidly declined as observed in influenza vaccine. Based on risk benefit analysis on individual basis varicella vaccine can be considered for a patient on TNFi, anti IL6 and anti IL1 agents. Further pediatric studies are may provide further guidance on the strength of recommendations for

certain vaccines in these patients.

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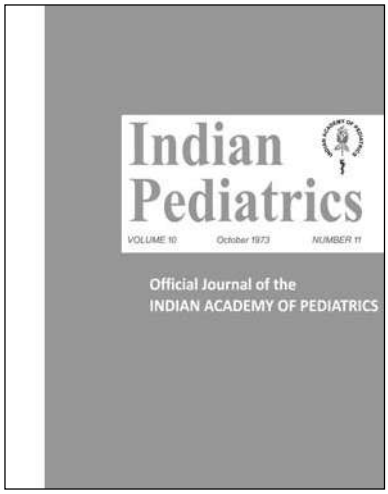
Cognitive Development in Children With Malnutrition: A 50-Year Tale

Bipul Kumar Das, Jaya Shankar Kaushik
Department of Pediatrics, All India Institute of Medical Sciences, Guwahati, Assam-781101
Correspondence: *Dr. Jaya Shankar Kaushik, Additional Professor, Department of Pediatrics, All India Institute of Medical Sciences, Guwahati, Assam 781101. jayashankarkaushik@gmail.com*

Globally, 145 million children under the age of 5 years are stunted, and 45 million are wasted [1]. Malnutrition is prevalent in India, with National Family Health Survey (NFHS-5) data indicating that stunting rates were 35.5% and wasting was 19.3% [2]. The relationship between malnutrition and intellectual performance has been a topic of great interest since the early 1980s. Several studies have demonstrated that children with malnutrition are at a higher risk of lower intelligence quotient (IQ) scores and perform poorly on attention, working memory, and visuospatial ability [3-9]. Stunted children are known to have a higher risk of lower IQ scores when compared to those with wasting [3]. Till two years of age, children have a high growth velocity and brain development. Malnutrition in this period adversely affects the children's brain development and, ultimately, the children's cognitive development. Rather, malnutrition in the first year of life affects personality development even at 40 years of life [10].



Malnutrition is assessed by anthropometric parameters, and the standards for comparison have shifted from Harvard standards to World Health Organization (WHO) growth charts based on Multicentre Growth Reference Study (MGRS) reference curves for children up to the age of 5 years. The correlation of anthropometric parameters with intelligence and cognitive performance has long been an area of interest.

THE PAST

A study was conducted 50 years back, during 1970-72, by Bhat, et al. [11], in 45 children with varying degrees of growth failure due to severe protein-calorie malnutrition. Children were classified into three groups – marasmic kwashiorkor, atrophic kwashiorkor, and sugar baby kwashiorkor with edema-free weight 40% or less, 30-40%, and 20-30%, respectively. The IQ or adaptive quotient (AQ) in the children was tested by using different tests (developmental screening inventory for infants, Gessel developmental schedule, VV Kamat revision of Binet intelligence scale, and Senguin Goddard form board). The physical growth of the children was assessed by comparing the weight and height of the kwashiorkor children in percentage to the 50th percentile of the Harvard standard. The height group was divided into four groups, and IQ was found to be increasingly more according to the increase in height percentile. Weight in the percentage of 50th percentile of Harvard standard was divided into five groups, and with an increase in weight percentile, the IQ was found to be higher. Children were divided into six groups according to their head circumference, and like in height and weight, the IQ was higher with an increase in head circum-ference percentile [11]. The authors men-tioned that growth failure was mainly of nutritional origin, and fetal malnutrition also played an essential role in the reduction in physical growth and head circumference [11].

THE PRESENT

Malnutrition, especially in early life, has significant and lasting implications for the development of cognition both in humans and animals [12]. Both prenatal (low birth weight) and postnatal malnutrition (stunting, low body weight) in babies have a negative influence on intellectual functioning in early school-aged children [4]. Protein-energy malnutrition with micronutrient deficiency and inappropriate social and familiar environments severely impede the full expression of poor children's genetic potential [13]. Even in preschool and school children, undernutrition negatively influences cognitive performance [5]. In a study by Kirkegaard, et al. [6], a higher IQ was seen with greater size at birth and more

significant weight gain in infancy among term babies. A greater height and head circumference growth throughout the first 5 years of life was also associated with higher childhood IQ in those children. A school-based study observed that children with stunting have 5.2 times lower IQ compared to those without stunting [7].

Traditionally, head circumference was often considered a surrogate marker of cognitive development. A systematic review including 12 studies revealed that malnutrition was associated with poor cognitive development [14]. Head circumference of less than the 10th percentile at birth in preterm babies less than 32 weeks of gestation is associated with poorer neurodevelopmental outcomes, independent of postnatal illness and white matter injury [15,16]. A similar association between head circumference and poor IQ was seen in older children aged 6 to 15 years [8,9]. In a study by Nicolaou, et al. [17], it was observed that there was no association between head circumference and cognitive, language, or motor skills. The study also revealed that the risk factors affecting head circumference, including maternal height, enrolment weight for age, and socioeconomic status, were similar to those affecting body length. Similar findings of poor relationship between head circumference and cognitive development have been observed by other authors, who believe these findings could arise from errors in head circumference measurement [18].

THE FUTURE

The concern of low IQ scores with malnutrition continues in the present, and is likely to continue in the future. Efforts to combat malnutrition and measures to adopt early intervention for better cognitive outcomes remain a significant priority in childhood development. The first 1000 days of life is the most crucial period of life as this is the period of rapid brain development, which starts immediately after conception. Any nutritional deficiency during this period i.e., from the time of conception to the age of two years, hampers brain development. The severity of the impact on brain development depends on the timing, chronicity, and severity of nutritional deficiencies [19]. The Supplementary Nutrition Programme under the Anganwadi Services and POSHAN Abhiyaan addresses the challenges of malnutrition in children, adolescent girls, pregnant women, and lactating mothers [20]. The government of India has established Nutritional Rehabilitation Centres (NRC) in different health facilities of the country under the National Health Mission (NHM) in order to provide facility-based management to children with severe acute malnutrition and to reduce under-five mortality due to severe acute malnutrition [21].

District Early Intervention Centres (DEIC) are the screening centers for children from 0 to 18 years of age; along with many other services, nutrition services are also provided with the help of a nutritionist/dietician or nursing staff to address the nutritional needs of children including identifying feeding skills, feeding problems, food habits, and food preferences [22]. About 43% of children from low- and middle-income countries (LMIC) under the age of 5 years are not expected to reach their developmental potential due to risk factors like poverty, stunting, and severe psychological deprivation, which have long-term effects on brain development and cognition [23].

The World Health Organization (WHO) and Indian Academy of Pediatrics (IAP) recommend the promotion of nurturing care for early childhood development (NC-ECD) in children up to 3 years of age by focusing on five essential components viz., good health, adequate nutrition, promotion of early childhood learning, responsive caregiving, and safety and security [24]. Nurturing care is a stable environment created by parents and other caregivers that ensures children's good health and nutrition and an emotionally supportive environment. The future will be an era of artificial intelligence and machine learning (AI/ML), and it will probably be easy to predict which baby will develop cognitive impairment based on AI tools. The use of AI/ML to identify and predict significant risk factors of malnutrition has already been documented. [25].

Protein-energy malnutrition (PEM) results in impairment in the cognitive functioning of children. With a gradual reduction in malnutrition and measures to combat malnutrition, we expect that future generations of children will not suffer from cognitive impairment or deficits secondary to malnutrition.

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EVENTS

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Jalandhar Academy of Pediatrics & IAP-Punjab
Dr Tarlochan Singh Randhawa, Organizing Secretary
9779027064; *Email*: info@sapapunjab.org;
Website: www.sapapunjab.org

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Contact:

Dr M Narayanan, Organizing Secretary
7012025938; *Email*: info@pedicon2024.com
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Kite String (*Manjha*) Injuries Among Children: Single Center Experience Over Four Years

We reviewed hospital records for kite-string injuries among children over four years (2017-2022). Of 42 affected children, mortality was 9.5%. The mean (SD) Pediatric Trauma Score (PTS) was 8.02 (2.66), with passively involved children facing greater severity [mean (SD) PTS, 5.58 (2.23)]. Kite-string injuries, alarmingly, endanger even bystanders, urging stricter preventive strategies.

Keywords: *Head injury, Mortality, Neck injury, Trauma.*

Kite flying, an integral part of Indian culture, is often associated with severe injuries due to a unique kite string known as *manjha* [1]. Coated with powdered glass or other sharp materials, intended to cut-through the kite strings of other kite-flyers, *manjha* results in a range of injuries from minor lacerations to serious deep tissue damage [1,2]. The danger associated with it are more pronounced in children, who lack the awareness or means to mitigate the associated risks [3]. Despite legal efforts to curb the use of the so-called "Chinese *manjha*" - a particularly sharp variant of this string, the incidence of these injuries is on the rise [4].

We performed a retrospective review at our level four trauma center in India, focusing on pediatric patients with kite string-induced injuries between 2017 and 2022. Forty two such cases (73.8% boys) were identified, with a median (IQR) age of 9.5 (5-11) years (**Table I**). Notably, an annual variance was observed: 16 in 2023, 12 in 2022, 8 in 2019, 2 in 2018, and 4 in 2017, and no cases between the years 2020 and 2021, possibly due to the pandemic related lockdowns. The patients were distinguished based on their involvement with kite flying: 12 (28.5%) passive (not involved directly in kite flying activity) and 30 (71.4%) active flyers. Passively involved cases had a more severe injury compared to active participants [mean (SD) Pediatric Trauma Score, 5.83 (2.75) vs 8.90 (2.20); *P*=0.001]. Non-participants had significantly higher intracranial injuries (53.3% vs 23.3%; *P*=0.030), intra-abdominal/thoracic injuries (50% vs 13.3%; *P*=0.012), tendon injuries (50% Vs 6.7%; *P*=0.001), and neck injuries (67.6 vs 26.7%; *P*=0.016) compared to active participants. Half (50%) of the children in active groups had only superficial cut wounds requiring only primary suturing, unlike their passive counterparts. Among 8 (19%) children with neck injuries, four (50%) patients required ligature of superficial vessels, 3 underwent internal jugular vein repair, and 4 (50%) required repair of trachea (9.5%). Overall, five patients (11.9%) required craniotomy for extradural hematoma and contusion, and four (9.5%) patients required laparotomy for pneumoperitoneum. Tube thoracostomy was performed in 6 (14.2%) cases of hemo-pneumothorax. We recorded four (9.5%) mortalities, two each in active (16%) and passive (6.6%) flyers. These patients had a mean (SD) PTS of 4.5 (1.7) and a Glasgow coma scale of 4.25 (1.3). In all cases, mortality happened within 72 hours of admission. All experienced polytrauma, with three (75%) succumbing to hemorrhagic shock and one (25%) to severe head trauma. Notably, all four children had a significant neck injury with tracheal involvement. Out of the total cases, we were able to monitor 26 (61%) patients for at least three months. While the facial lacerations healed adequately with primary suturing, significant permanent residual scarring was observed in all. Of the 11 patients who survived having head trauma, five (45.5%) children presented with notable residual neurological deficits at mean (SD) follow-up duration of 2.57 (1.39) years.

In 85% of the cases where the type of kite string was identified, the string was the banned Chinese *manjha* with nylon-like thread with higher tensile strength, compared to a normal thread, and coated with powdered glass [3]. None of the children had protective measures like safety protocols or protective gear.

Kite flying, integral to Indian culture, faces regulatory challenges While the 1934 Indian Aircraft Act imposed restrictions for aviation safety, many remain unaware. In a significant judgment, the Delhi High Court declined to impose a kite-flying ban in the National Capital Region (NCR), citing cultural reasons [5]. Previous studies have also reported a higher incidence of head and neck injuries in these children which are considerably severe [3,4]. Direct injuries to the kite flyers have been reported predominantly. In our study, we found that children who are not involved in kite flying injuries are also at risk, even more for severe injuries. Previous studies have highlighted the possible mechanisms, which may be entangled while moving at a fast speed like a bike [2]. Associated injuries were more common in children, and primarily resulted from falls from height while attempting to fly or catch kites. This could be attributed to children's excitement and lack of awareness to mitigate the risks [6,7].

The severity of kite string injuries we observed, especially in passive bystanders, are alarmingly severe and might only be the tip of the iceberg, as many children who sustain minor to critically serious injuries might never be brought to hospital. Given the heightened risks to

uninvolved individuals, there is an urgent need for heightened public awareness, parental education, safety measures, and stricter legislation against hazardous materials like Chinese *manjha*.

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PREETI TIWARI,[1] NISHTHA CHAUHAN,[2] RAHUL PATEL,[3] RATHINDRA NATH BERA,[4] VAIBHAV PANDEY[5]*
[1]Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi, Uttar Pradesh.
[2]Oral and Maxillofacial Surgery, Trauma Center, IMS-BHU, Varanasi, Uttar Pradesh.
[3]Department Of Orthopedics, Trauma Center, IMS-BHU, Varanasi, Uttar Pradesh.
[4]Oral and Maxillofacial Surgery, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand.
[5]Department of Pediatric Surgery, IMS-BHU, Varanasi, Uttar Pradesh.
**vaibhavpedbhu@gmail.com*

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District-Wise Treatment Gaps and Hospitalizations in Under-Five Children With Diarrhea in India

India bears greatest under-5 diarrheal burden and mortality. We studied geographical variation in under-5 diarrhea prevalence, oral rehydration solution (ORS) and zinc supplementation treatment gaps and hospitalization rates. We point to treatment gap in western Maharashtra, Andhra Pradesh and Gujarat. Diarrheal hospitalization rates were not significantly associated with ORS and zinc treatment gaps.

Keywords: *Dehydration, ORS use, Zinc.*

India ranks second in under-5 diarrheal disease burden and mortality [1]. Diarrhea is India's third leading cause of under-5 mortality [2]. Oral rehydration solution (ORS) and zinc can avert 93% of diarrheal deaths [3,4]. Depending on severity, diarrhea may need healthy facility visits/ hospitalizations. The ORS and zinc utilization rate for under-5 diarrhea in India is 60.6% and 30.5%, respectively [5]. The ORS and zinc utilization, health facility visits, and hospitalizations vary across Indian districts. However, these geographic variations have not been studied yet. Understanding geographical differences in health-seeking behavior for under-5 diarrhea can help target interventions to increase the uptake of ORS and zinc in low utilization areas and divert health system resources to high hospitalization areas. Our study thus had three aims: Measure district-wise treatment gap (TG) for ORS and zinc in under-5 diarrhea; Study district-wise health facility visits and hospitalization rates in under-5 diarrhea; and, analyze the association of ORS and zinc TGs with health facility visits and hospitalization rates across districts.

We conducted a cross-sectional retrospective secondary- data analysis for 2019-20 using National Family Health Survey (NFHS) 5 - Phase 1 and Health Management and Information System (HMIS). Details on data sources are given in **Web Annexure I**.

We extracted district-wise percentages of prevalence of diarrhea in under-5 children, children receiving ORS and zinc each, in the two weeks recall period from NFHS-5. Raw treatment gaps (TG_R) were defined as the percentage of children with diarrhea who did not receive ORS and zinc.

ORS $TG_R = 100 - (\%\ under\text{-}5\ children\ received\ ORS)$

Zinc $TG_R = 100 - (\%\ under\text{-}5\ children\ received\ Zinc)$

Districts were ranked (r_p) in descending order of under-5 diarrhea prevalence and weights (W_p) were calculated by dividing district's prevalence rank by the sum of all ranks.

$$W_p = \frac{\gamma_p}{\Sigma\gamma_p}$$

Prevalence-weighted treatment gap (TG_W) was calculated by multiplying TG_R with W_P.

$$TG_W = W_p * TG_R$$

TG_W was scaled (TG(scaled)$_W$) from 0 to 100 using min-max scaling.

$$TG\,(scaled)_w = \frac{[TG_W - TG\,(min)_W]}{[TG\,(max)_W - TG\,(min)_W]}$$

Six ORS and zinc TG groups were created using the targets suggested for Indian states by Clinton Health Access Initiative [6]. TG(scaled)$_W$ was used to classify districts into these groups (**Web Table 1**).

HMIS data was used to calculate district-wise under-5 diarrhea hospitalization rate.

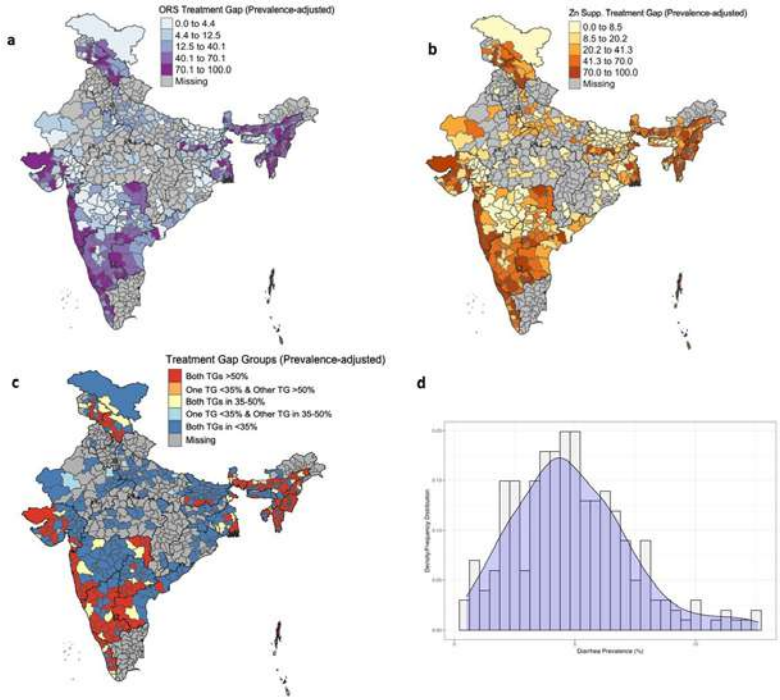
$$Diarrhea\ \ hospitalization\ \ rate = \frac{No.\ of\ under\text{-}5\ children\ received\ inpatient\ treatment\ for\ diarrhea}{No.\ of\ under\ -5\ children\ with\ diarrhea} \times 100$$

We evaluated if health facility/provider visits and diarrhea hospitalization rates varied across TG groups. All analyses were conducted for scaled and raw TG groups. Details on data availability are given in **Web Annexure I**.

The western Maharashtra, Andhra Pradesh, and Gujarat, North Eastern states, Kerala, and Karnataka had districts with high (>40%) ORS and zinc TG(scaled)$_W$ **(Fig. 1a, b)**. The district distribution across TG groups based on TG(scaled)$_W$ is given in **Fig. 1c** (**Web Table I)**. Further, 242 districts with under-5 diarrhea prevalence ranging from 1%-10% had no ORS or zinc utilization and no health facility visits indicative of the true TG **(Fig. 1d)**. District-wise diarrhea prevalence, ORS TG_R, Zinc TG_R, and distribution across TG groups based on TG_R are presented in **Web Fig. 1-4.** State-wise match rate in TG groups assigned using TG(scaled)$_W$ and TG_R is given in **Web Fig. 5**.

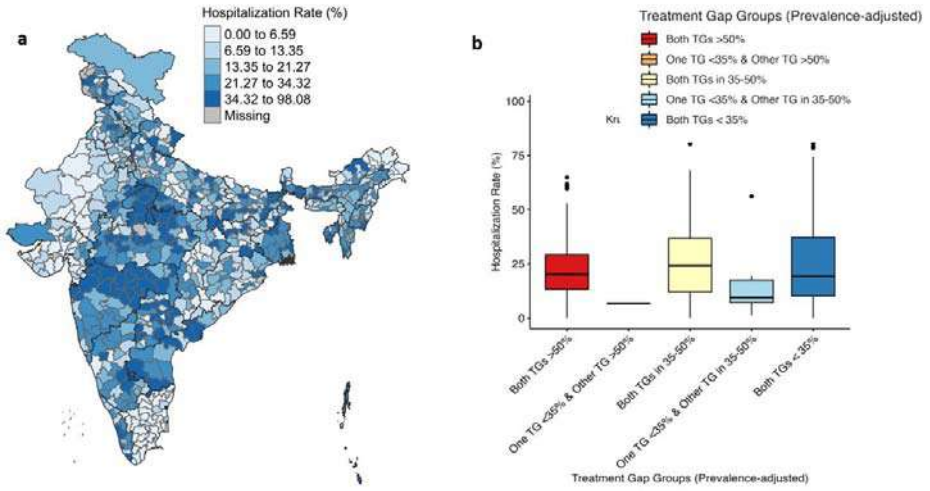
The hospitalization rate was high (>34%) in central India districts, especially in eastern Maharashtra and northern Madhya Pradesh **(Fig. 2a)**. District-wise health facility/provider visits can be seen in **Web Fig 6**. Diarrhea hospitalization rates and health facility/provider visits were not significantly associated with TG(scaled)$_W$- or TG_R-based TG groups (**Fig. 2b , Web Fig. 7-9**).

The study presents a systematic district-level analysis of diarrhea treatment modalities that can help identify priority districts for interventions targeted to increase ORS and zinc uptake. ORS and zinc TGs vary across Indian districts with



Prevalence-adjusted treatment gap is the same as TG(scaled)$_W$. ORS: oral rehydration solution.

Fig. 1 District-wise treatment gaps for the year 2019-20, *a*) scaled-weighted treatment gap of ORS for 457 districts, *b*) scaled-weighted treatment gap of zinc for 457 districts, *c*) Treatment gap groups based on scaled-weighted treatment gap for 457 districts, *d*) True treatment gap for 242 districts.



Prevalence-adjusted treatment gap is the same as TG(scaled)$_W$. TG: treatment gap.

Fig. 2 Hospitalization rate and treatment gap groups *a*) District-wise diarrhea hospitalization rate for 724 districts, *b*) Association of hospitalization rates with scaled-weighted treatment gap groups for 457 districts.

over one-third of districts falling in the high-priority group. The findings can also assist in the optimal allocation of health-system resources to districts with higher hospitalization rates. However, these findings must be interpreted with caution as the TG for several districts could not be calculated due to a lack of data.

Ethics approval: Not applicable.
Contributors: SD conceptualized the study design, acquired, analyzed, or interpreted data, drafted the manuscript, and critically revised the manuscript for important intellectual content. DS acquired, analyzed, or interpreted data, and drafted the manuscript VW acquired, analyzed, or interpreted data, and drafted the manuscript. SZ - conceptualized the study design, drafted the manuscript, critically revised the manuscript for important intellectual content, provided administrative, technical, or material support, and supervised the study. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

SWETA DUBEY,[1,2] DIVYA SHRINIVAS,[1,3] VIDHI WADHWANI,[1,4] SIDDHESH ZADEY[1,5*]
[1]Association for Socially Applicable Research (ASAR), Pune, Maharashtra, India.
[2]Department of Pediatrics, SUNY Downstate Health Science University, New York, US.
[3]Swami Ramanand Teerth Rural Government Medical College, Ambajogai, Maharashtra, India.
[4]Gujarat Cancer Society (GCS) Medical College, Hospital and Research Centre, Ahmedabad, Gujarat, India.
[5]Dr DY Patil Medical College, Hospital, and Research Centre, Dr DY Patil Vidyapeeth, Pune, Maharashtra, India.
**sidzadey@asarforindia.org*

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Web Annexure I

SUPPLEMENTAL METHODS

Data sources details

We accessed data from the National Data Analytics Platform (NDAP) to conduct a retrospective secondary data analysis for the year 2019-2020. From the NDAP, we extracted data from two sources - the first wave of the National Family Health Survey (NFHS) 5 covering June 2019- January 2020 and the Health Management and Information System (HMIS) covering the financial year 2019-20. NFHS is a nationally representative household survey and HMIS reports routine health facility data.

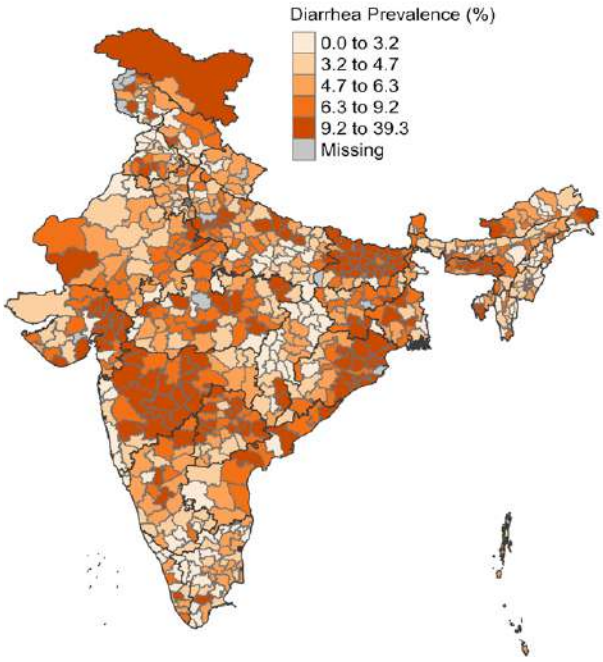
Data availability

Out of 733 districts used in the analysis, the percent prevalence of under-5 diarrhea data was available for 728 (99.3%) districts. The percentage of under-5 children who received ORS and zinc and visited a health facility/ provider was available for 457 districts. Thus, treatment gaps (both raw and scaled-weighted) were calculated for only 457 (62.3%) districts. The hospitalization rate was calculated for 724 (98.8%) districts.

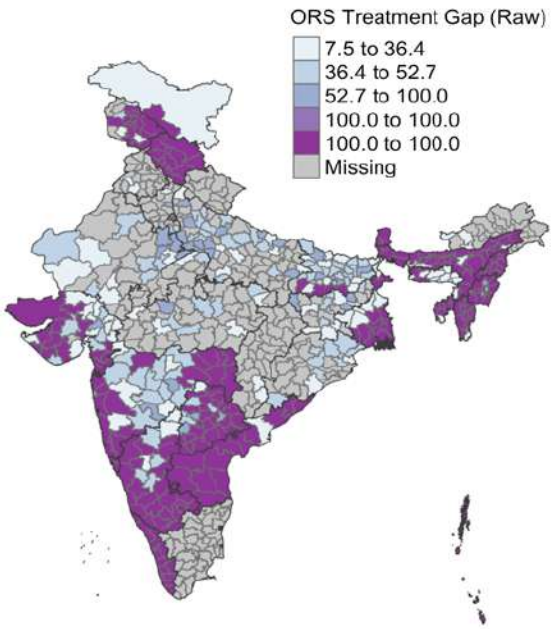
Web Table 1 Treatment Gap Groups Used to Classify 457 Districts based on ORS and Zinc Treatment Gaps. ORS: Oral Rehydration Solution

Treatment gap group	*ORS treatment gap*	*Zinc supplementation treatment gap*	*Number of districts in the group*
1	>50%	>50%	155
2	>50%	35%-50%	0
	35-50%	>50%	0
3	<35%	>50%	1
	>50%	<35%	1
4	35%-50%	35%-50%	47
5	35%-50%	<35%	6
	<35%	35-50%	6
6	<35%	<35%	248

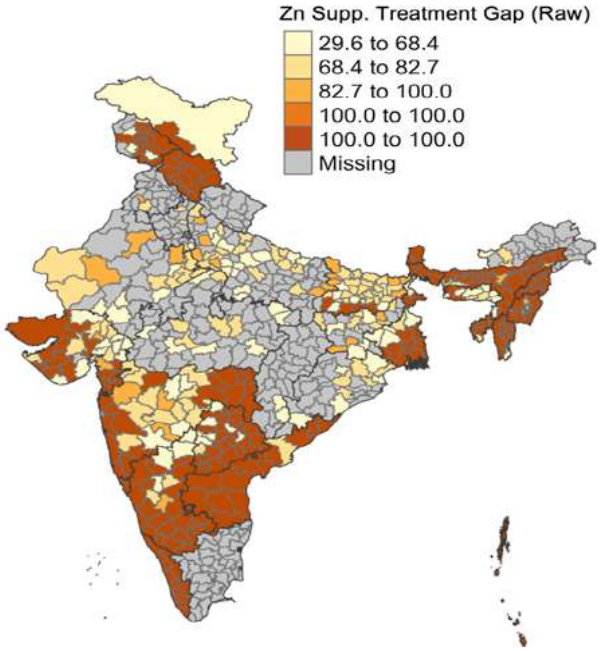
Districts in the first group had the highest need for diarrheacare intervention.



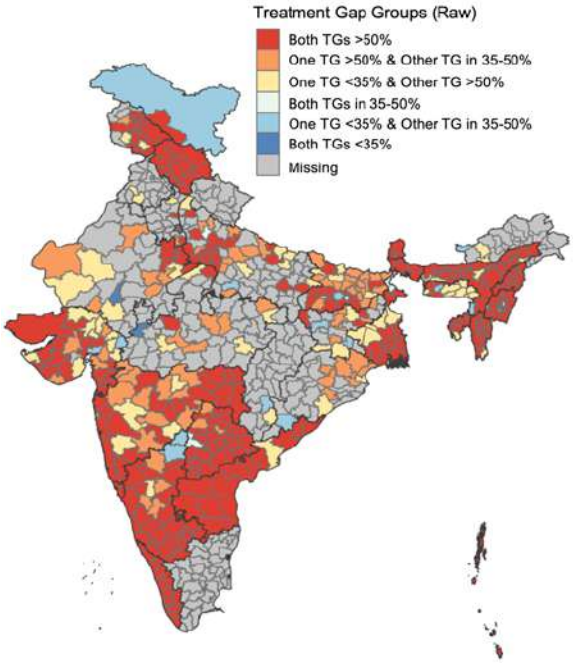
Web Fig. 1 District-wise diarrhoea prevalence for 728 districts of India, 2019-20.



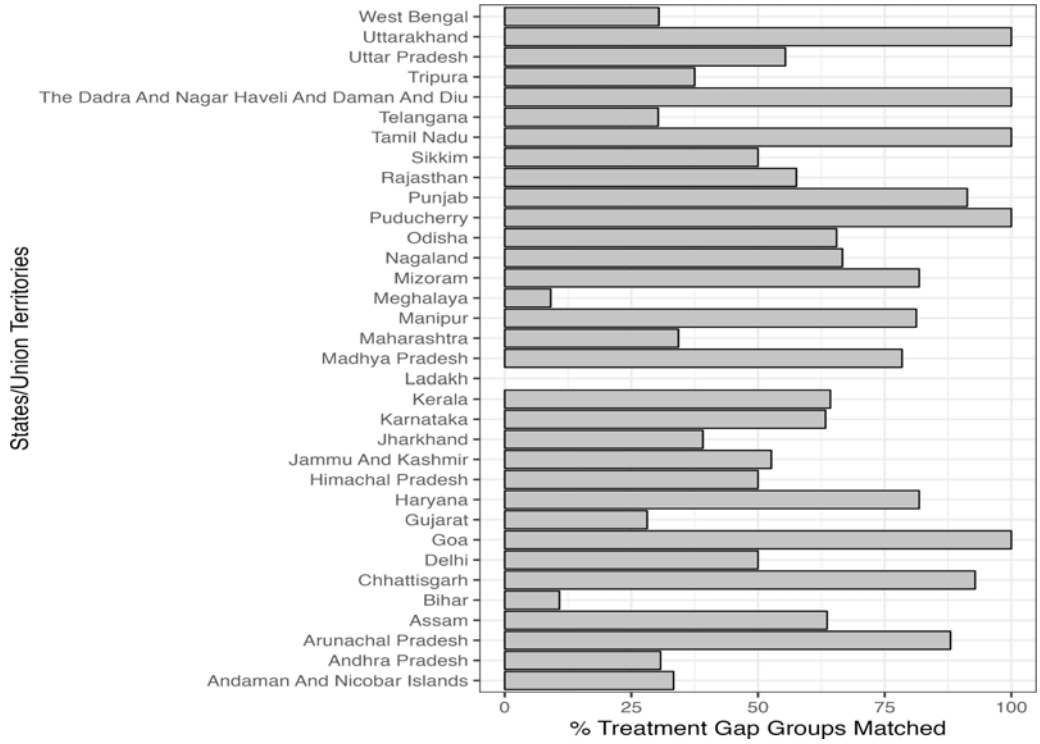
Web Fig. 2 District-wise raw Oral rehydration solution (ORS) treatment gap for 457 districts of India, 2019-20.



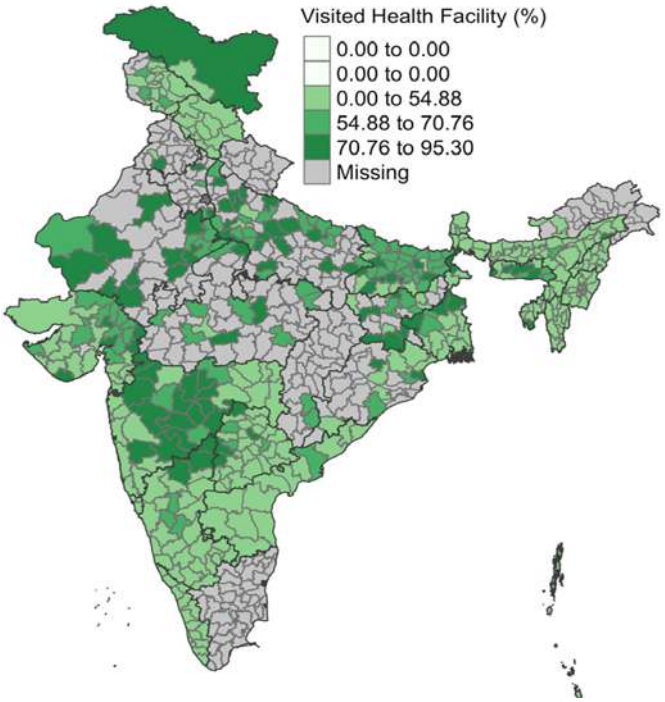
Web Fig. 3 District-wise raw zinc treatment gaps for 457 districts of India, 2019-20.



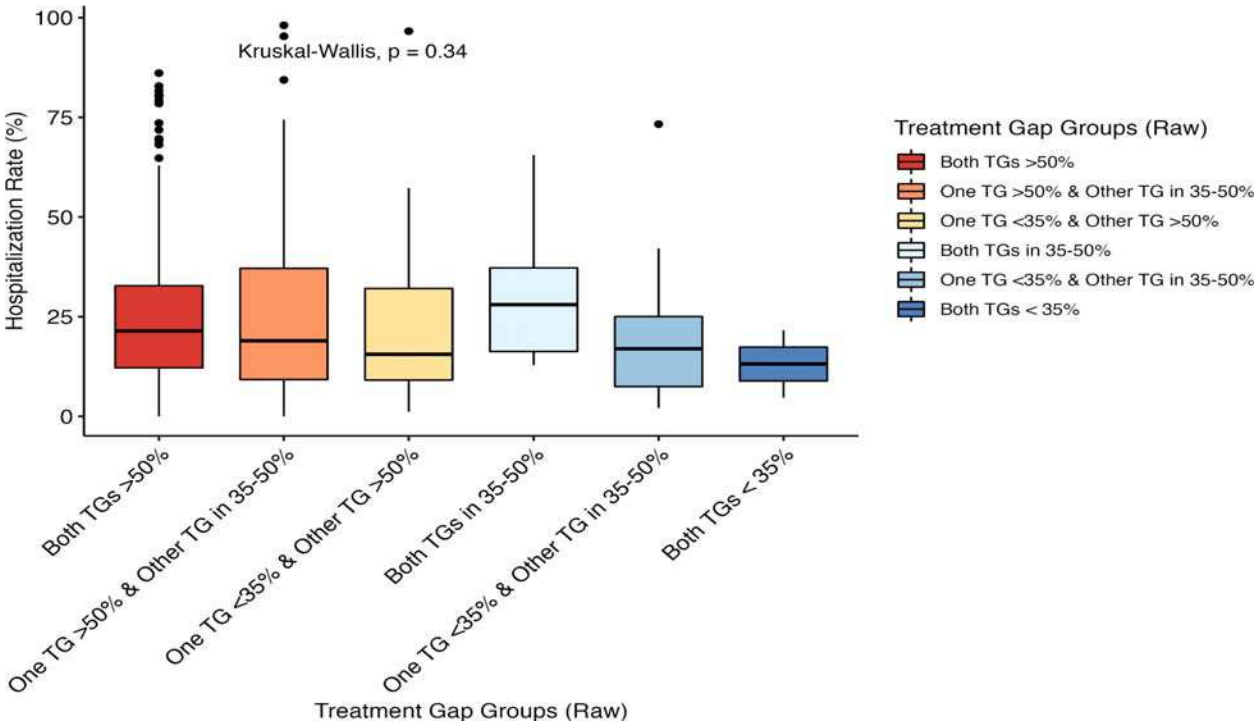
Web Fig. 4 Treatment gap groups based on raw ORS and zinc treatment gaps of 457 districts of India, 2019-20.



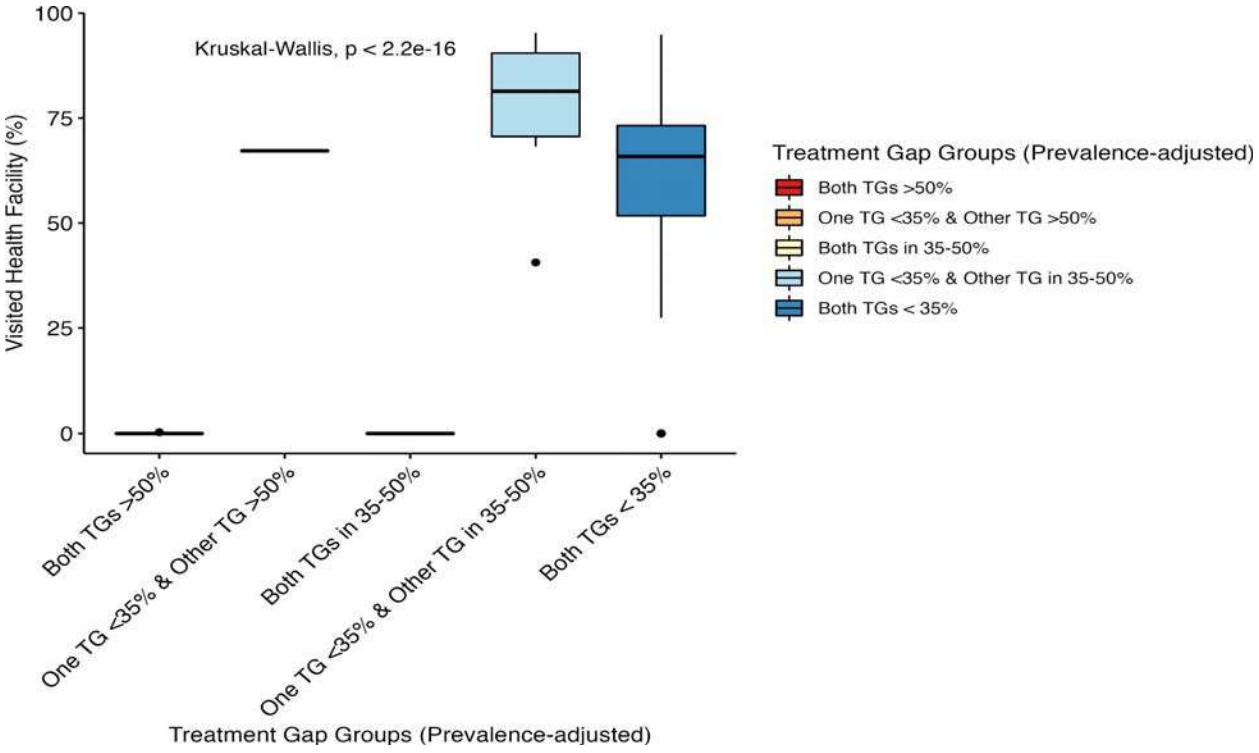
Web Fig. 5 State-wise match rate in treatment gap groups assigned using scaled-weighted and raw treatment gap.



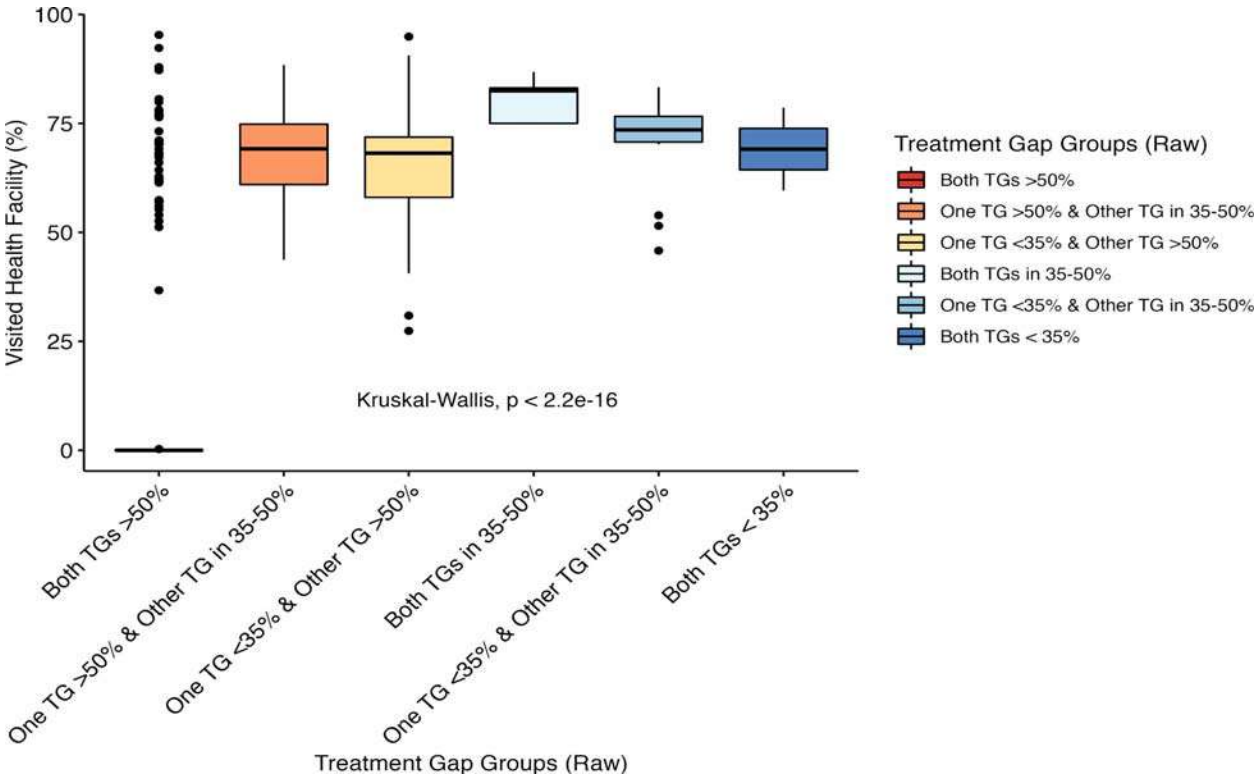
Web Fig. 6 District-wise health facility/provider visited for 457 districts of India, 2019-20.



Web Fig. 7 Association of hospitalization rates with raw treatment gap groups for 457 districts



Web Fig. 8 Association of health facility/provider visits with scaled-weighted treatment gap groups for 457 districts



Web Fig. 9 Association of health facility/provider visits with raw treatment gap groups for 457 districts

Cutaneous-Visceral Loxoscelism With Delayed Hemolysis in an Adolescent

Arthropods bites and stings are common presenting complaints in the pediatric emergency. Spider bites are rare and symptoms may vary from subtle to life threatening clinical presentation depending on the species. Loxoscelism is the constellation of clinical features produced by the bite of spiders belonging to the genus *Loxosceles*, commonly known as recluse spiders. We herein report an adolescent boy who presented with severe loxoscelism.

CASE REPORT

A 14-year-old boy presented with history of a brown spider bite over the left side of his chest while cleaning the house five days ago. He developed a rash on the same day over the bite site, which was pruritic and erythematous and gradually progressed all over the body. The lesion at the bite site progressed to a blackish necrotic lesion, for which debridement was done at an outside hospital on day three of rash onset (**Fig. 1a**). He was given intravenous antibiotics and oral steroids at a nearby hospital for three days. He presented to our hospital on day five with yellowish discoloration of the face, myalgia, worsening of rashes and persistent fever. At arrival, his heart rate 120/minute, respiratory rate 24/minute, blood pressure 72/42 mmHg, and SpO_2 was 94% in room air. On examination, he had an exanthematous eruption of multiple maculopapular lesions over the entire body, sparing the head and neck (**Fig. 1b**). The rest of the systemic examination was normal. He was resuscitated with a fluid bolus followed by empirical antibiotics (ceftriaxone, vancomycin and doxycycline) considering secondary disseminated *Staphylococcus* sepsis and rickettsial infection. Other considerations were drug-induced anaphylaxis and loxoscelism. Antihistaminics (H1- and H2-blockers) and topical emollients were also added. Shock improved with fluids bolus and did not require any inotropic support. Species identification was done by showing pictures of different spiders to the child and parents.

Investigations revealed hemoglobin of 7g/dL, total leukocyte count of 9850/mm^3, platelets 1.9 lakhs/mm^3, and reticulocyte count 5.32%. Serum biochemistry revealed normal urea and creatinine, and an elevated total bilirubin

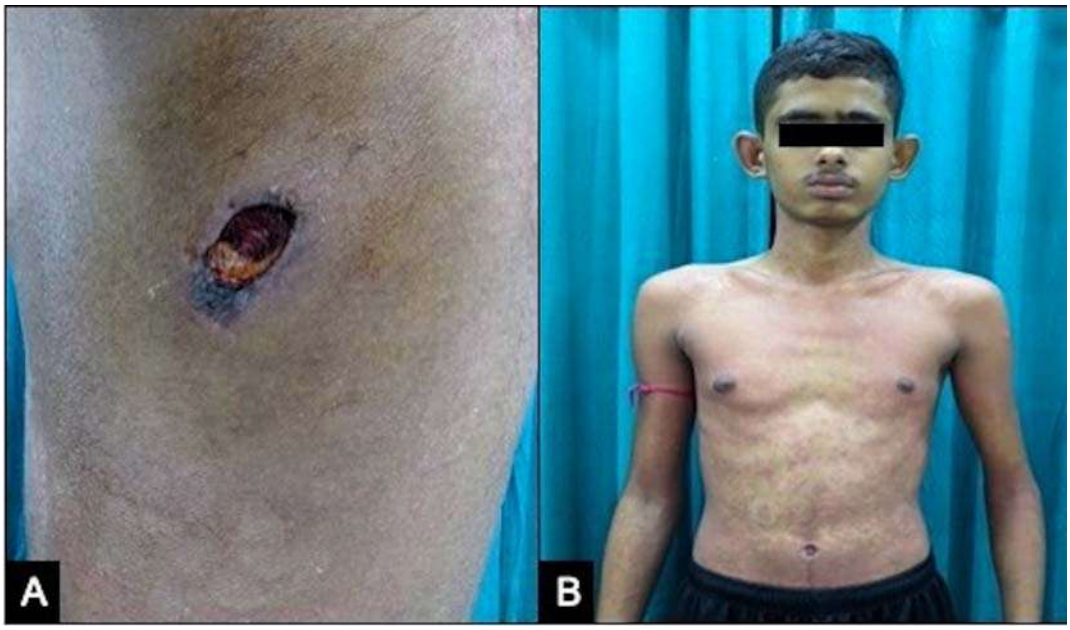


Fig. 1 *a*) Post-debridement bite site surrounded with erythematous macules and *b*) confluent blanchable erythematous maculopapular lesions over the trunk and upper extremities, sparing head and neck.

of 8.03 mg/dL (direct bilirubin of 0.43 mg/dL), with normal aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Coagulogram revealed normal prothrombin time of 15.9 seconds, thromboplastin time of 27 seconds, and fibrinogen levels of 402 mg/dL. The blood culture was sterile. The inflammatory markers were elevated with C-reactive protein (CRP) 53.5 mg/L and procalcitonin 2.23 ng/mL. Lactate dehydrogenase (LDH) level was elevated (612 U/L). The direct antiglobulin test (DAT) was negative. Glucose-6-phosphate dehydrogenase (G6PD) level was 21.7 (6.4-18.7) U/gm Hb. Scrub typhus serology was negative. He improved symptomatically, remained hemodynamically stable during the hospital stay of 7 days, and was discharged on topical antibiotics for dermal necrosis and antihistamines. He came for follow-up after one week, by when scar had healed, and jaundice had improved.

The index child had a bite from a brown recluse spider (*L. reclusa*). This envenomation results in severe local reactions, including dermonecrosis, ulceration, abscess, acute hemolytic anemia, disseminated intravascular coagulopathy (DIC), rhabdomyolysis, acute kidney injury, and even death [1-3]. The systemic symptoms may include fever, headache, nausea, and muscle pain. Only systemic symptoms without skin necrosis are infrequent in loxoscelism [2]. The pathogenesis is that the sphingomyelinase in loxosceles venom induces complement-dependent dermonecrosis, neutrophil infiltration, and endogenous gelatinase expression [4]. The other venom components include collagenases, hyaluronidases, and peptidases.

The less recognized hematological manifestations of acute hemolytic anaemia due to loxoscelism were pre-viously reported in six adolescents [5]. Few cases of cutaneous loxoscelism have been reported in Indian children [3,6], but cutaneous-visceral or cutaneous-hemolytic loxoscelism has not been reported. The pathophysiology of loxoscelism-associated hemolysis is poorly understood, but the postulated mechanism is the lysis of erythrocytes induced by sphingomyelinase in the loxosceles venom [5]. The alternate complement pathway is activated due to adamlysin family metalloproteases resulting in the cleavage of sialic-acid rich surface red blood cell (RBC) glycophorins A,B,C [2,5]. The anemia in loxoscelism is due to direct toxin-related RBC damage and complement-mediated immune destruction [5]. A previous review [2] reported that 74% patients had cutaneous loxoscelism, and 26% had cutaneous-hemolytic form. They also observed that 71.6% of the patients with loxoscelism developed necrosis [2]. Another literature review [2] found that 26% has hemolytic anemia, 14% had acute renal failure, 4% had thrombocytopenia, and 2% had DIC.

The management for loxoscelism reported in the literature includes antibiotics, dapsone, antihistamines, steroids, blood transfusions, intravenous immunoglobulin (IVIg), and surgical debridement [1,2]. The other therapies used include hyperbaric oxygen therapy, dialysis, skin grafting, antivenom therapy, and therapeutic plasma exchange [2]. Prompt medical attention is crucial to prevent complications and promote recovery. Public awareness is needed for possibility of systemic effects of spider bites, and need for early medical case for the same.

PRADEEP KUMAR GUNASEKARAN,[1] BHARAT CHOUDHARY,[2*] MEGHA PATEL,[1] SAURABH SINGH [3]

[1]Department of Pediatrics, All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan.

[2]Department of Trauma and Emergency (Pediatrics), AIIMS, Jodhpur, Rajasthan.

[3]Department of Dermatology, Venereology and Leprosy, AIIMS, Jodhpur, Rajasthan.

**drbharatpaeder@gmail.com*

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Antivirals for Childhood Type 1 Diabetes

Globally the incidence of non-communicable diseases including diabetes is increasing with time. There is 39% increase in the childhood diabetes cases over a 3-decade period between 1990 and 2019. With improved accessibility to health care, the number of diabetes related deaths has reduced across the world, but still the number is huge. Childhood diabetes possess a significant challenge in front of parents as well as the healthcare system due to the associated acute and late multisystemic complications.

Multiple factors like genetic makeup, altered immune system and environment play an important role in the pathogenesis of type-1 diabetes. Studies have implicated the role of various viruses, especially enteroviruses, in the development of auto-antibodies against the pancreatic islet cells, leading to the development of type-1 diabetes. In a recently published, phase 2, placebo-controlled, randomized, parallel group, double-blind trial, researchers have studied the role of antiviral treatment for preserving the pancreatic beta-cell function. In this study, 96 children aged between 6-15 years with new onset type 1 diabetes were divided into two groups: treatment group receiving pleconaril and ribavirin (n=47), and placebo group (n=49) and started on the intervention within three weeks of diagnosis. Mean stimulated C-peptide area under the curve (AUC) after twelve months of treatment was estimated for assessing the pancreatic beta cell function, which was higher in the antiviral treatment group compared to the placebo group. These findings highlight the need for exploration of the role of antivirals in the management of children with new-onset type 1 diabetes. (*Nature Medicine 04 October, 2023*)

Emerging Threat of Artemisinin-resistant Malaria

Malaria can result in serious life-threatening complications unless promptly diagnosed and treated. In 2021, there were 247 million cases of malaria globally, countries from African region accounts for almost 95% of cases and 96% of deaths. Artemisinin-based combination therapy (ACT) are the main drugs for the treatment of *Plasmodium falciparum* malaria. During the last decade, there were reports about the partial artemisinin resistance from the Greater Mekong subregion in Southeast-Asia, resulting in persistence of parasites three days after the initiation of artemisinin-based combination therapy. Recently, there are reports from Rwanda and Uganda about the emergence of partial resistance to artemisinin in *P falciparum*, threatening the efforts to control malaria in the African region. A group of researchers analyzed the data of three unpublished drug-efficacy studies conducted in 2016, 2017 and 2019, respectively to determine the presence of clinical partial resistance to ACT by assessing the proportion of cases with persistence of parasites 3 days after the initiation of artesunate–amodiaquine or arte-mether–lumefantrine treatment. Presence of Pfkelch13 mutation in the parasite was used as a predictive marker of partial resistance to artemisinin. The results of analysis showed that the odds of persistence of parasite positivity on day three of ACT has increased by a factor of 6.2 (95% confidence interval, 2.5 to 15.5) among the patients with Pfkelch13 622I variant parasites between 2016-2019. Among those with Pfkelch13 R622I mutation, 16.9% also carried deletion mutations in both hrp2 and hrp3, making it difficult to detect these cases by HRP2-based rapid diagnostic tests. Detection of partial artemisinin resistance in two unrelated related areas is a matter of serious concerns for all of us, as in the present times there is no alternative to ACT against malaria. (*NEJM 28 September, 2023*)

Second Anti-Malarial Vaccine

In October 2021, the World Health Organization (WHO) had recommended the first antimalarial vaccine - RTS,S/AS01, for its widespread use among the children living in the sub-Saharan Africa and other regions with moderate to high prevalence of *P. falciparum* malaria. Despite this recommendation, the countries of African region are facing a high burden of malaria, and limited supply of vaccine is the main reason. In order to solve this issue, recently the WHO strategic advisory group of experts on immunization (SAGE) and the malaria policy advisory group (MPAG) have recommended another vaccine for use in African children. R21/Matrix-M is the second antimalarial vaccine recommended by WHO for use in malaria endemic areas with high disease burden. R21/Matrix-M vaccine contains two components-R21 antigen, which is specific to the malaria parasite, and Matrix-M, a saponin-based adjuvant that enhances the immune response and durability of vaccine. The results of phase III clinical trial, involving 4,800 children from four African countries (Burkina Faso, Kenya, Mali and Tanzania) showed an efficacy of 75% against sites with high seasonal malaria transmission and 68% at the sites with more perennial transmission during a period of 12 months following a 3-dose series. Booster dose twelve months after the third dose helped in maintaining the efficacy. It had been well tolerated by the recipients and had a good safety profile. (*WHO.int 02 October, 2023*)

Nobel Prize in Physiology or Medicine 2023

This years, Nobel Prize in Physiology or Medicine has been jointly awarded to Katalin Karikó and Drew Weissman for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19. Antiviral vaccines developed from killed or attenuated viruses, subunit or vector-based vaccines are available for a long time. But these methods require large-scale cell culture mediums and significant time, which makes them unsuitable for vaccine production during outbreaks and pandemics. In vitro transcription of mRNA is the answer to all these problems but initially it was associated with challenges like instability of the molecules, difficulty in their delivery, and inflammatory reactions by host. The discovery of nucleoside base modifications in the mRNA by Katalin Karikó and Drew Weissman helped reducing the inflammatory reactions and increase the protein production when mRNA is delivered to cells. Their research showed that base-modified mRNA can be used to block the activation of an enzyme that regulates protein production, and to stimulate the formation of an immune response to a particular pathogen. As result of this discovery, rapid and flexible vaccine production in response to outbreaks and pandemics is possible. This enabled the development of effective mRNA vaccines against COVID-19 and other infectious diseases. (*Nobelprize.org 02 October, 2023*)

RAJESH KUMAR MEENA
raj.mamc@gmail.com

Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review (J Infect Public Health. 2023;16:660-72)

The World Health Organization (WHO) has recently established a consensus definition for long COVID, characterizing it as symptoms persisting for at least 2 months, usually occurring 3 months after the onset of COVID-19, with no alternative diagnosis to explain the symptoms. While long COVID has been observed in adult patients, its prevalence and characteristics in pediatric cases is not well-understood. A systematic review was conducted following MOOSE and PRISMA guidelines including studies on the prevalence of long COVID and its associated risk factors in pediatric COVID-19 survivors. The key findings of the review included that the pooled prevalence of any long COVID in pediatric survivors was 23.4%, with generalized symptoms being the most common (19.6%), followed by respiratory (14.8%), neurologic (13.5%), and psychiatric (12.3%) symptoms. Specific symptoms such as dyspnea (22.7%), fatigue (20.2%), and headache (15.9%) were frequently reported. The prevalence of symptoms varied with the duration of follow-up, with higher rates seen in the first 3-6 months post-infection. Factors associated with a higher prevalence of long COVID included age over ten years, multisystem inflammatory syndrome, severe clinical symptoms, older age, female gender, poor physical or mental health, severe infection, and a higher number of initial symptoms. Several risk factors were identified, including older age, female gender, poor physical or mental health, severe symptoms during the acute phase, longer hospitalization, specific organ involvement, and more initial symptoms. Author concluded that nearly one-quarter of pediatric COVID-19 survivors experienced multisystem long COVID even a year after infection. The study underscores the need for ongoing monitoring, prevention, and intervention for pediatric survivors, particularly those with high-risk factors. These findings emphasize the importance of managing both the physical and psychological aspects of long COVID in pediatric patients.

Longitudinal cardiac outcomes of multisystem inflammatory syndrome in children: A systematic review and meta-analysis (Pediatr Cardiol.2023 44:892-907)

A dearth of extensive longitudinal data on cardiac outcomes in children suffering from multisystem inflammatory syndrome (MIS-C) linked to COVID-19 prompted this systematic review and meta-analysis, with a goal to explore the mid-term cardiovascular prognosis for children affected by MIS-C, shedding light on the condition's long-term outlook. Examining data from eleven observational studies with a follow-up period (3 months to 1 year), published between 2021, and 2022, which included a total of 547 MIS-C patients. Data extraction involved two researchers, and longitudinal outcomes were synthesized using a one-group meta-analysis employing a random-effects model. They reported a mortality rate of 2.5% (95% CI 1.3-4.9) among MIS-C patients, suggesting a relatively low risk of death associated with the condition. In the acute phase of MIS-C, 46.8% (95% CI 32.7-61.3) of patients experienced left ventricular (LV) systolic dysfunction. However, the majority of these cases resolved within 3 months, with only 1.7% and 2.1% of patients still experiencing mild LV systolic dysfunction at 3 and 6 months, respectively. At the outset, 23.7% (95% CI 17.7-31.1) of MIS-C patients exhibited coronary abnormalities such as coronary artery dilatation or aneurysms. While many of these cases resolved, 4.7% (95% CI 1.5-14.3) and 5.2% (95% CI 3.0-8.9) of patients still had persistent coronary abnormalities at 3 and 6 months, respectively. Mitral regurgitation (MR) was observed in 56.6% (95% CI 27.7-81.6) of patients at baseline. However, 7.5% of patients continued to experience MR at the 6-month follow-up. Therefore, this study concluded that the mid-term cardiovascular outcomes of MIS-C in children, had a relatively low mortality rate and favorable recovery of LV systolic dysfunction in most cases. However, the persistence of coronary abnormalities and MR in some patients highlights the importance of continued monitoring and research in this area to better understand and manage MIS-C over the long term.

Childhood and adolescent television viewing and metabolic syndrome in mid-adulthood (pediatrics. 2023 152: e2022060768**)**

This study investigates whether childhood television viewing habits are associated with an increased risk of developing metabolic syndrome at age 45. The research focuses on a birth cohort from Dunedin, New Zealand, born in 1972 and 1973. Initially comprising 1037 children, this cohort has been continuously monitored, with 938 surviving members assessed at age 45. The study collected data on television viewing habits at ages 5, 7, 9, 11, 13, 15, and 32, constructing a composite measure of childhood and adolescent television viewing. It also recorded height and weight at age 5 to calculate BMI and assessed physical activity levels at age 15. At age 45, participants' height, weight, waist circumference, blood pressure, and cardiorespiratory fitness (V'O2 max) were measured. Blood samples were analyzed for metabolic parameters, and metabolic syndrome was diagnosed based on specific criteria. Metabolic syndrome, associated with cardiometabolic risk factors like obesity, insulin resistance, and high blood pressure, was found in 20% of women and 34% of men. The study revealed that childhood television viewing between ages 5 and 15 was linked to an increased risk of metabolic syndrome at age 45. This association remained even after adjusting for gender, childhood BMI, socioeconomic status, and adult television viewing. Childhood television viewing was also associated with higher BMI, lower cardiorespiratory fitness, larger waist circumference, and higher blood pressure at age 45, primarily among women. It highlights the need for interventions aimed at reducing screen-based activities among children and youth to promote long-lasting health benefits.

RAJESH KUMAR
mdpedrajesh@gmail.com

Experience of Health Professionals in the Kongpopki District of Manipur

Manipur has been caught up in an ethnic conflict since May, 2023. This has led to an internal displacement of roughly 50,000 persons [1]. Displaced persons have been housed in relief camps in educational institutions in the state and some neighboring districts. The authors were deputed by their institution for 15 days, to provide healthcare services at some relief camps and at the Kongpokpi district hospital. The district of Kongpokpi had no regular pediatrician, according to the information provided by the staff nurse in the district hospital, who conveyed that medical officers were addressing all child health concerns. There is one pediatrician in the nearby district of Senapati who is often consulted if there are any sick babies who require referral.

Each of us evaluated 30-40 children with various ailments at the district hospital daily. Most had respiratory infections, diarrheal diseases, skin infections, and eye flu. We observed that many parents had started oral antibiotics for their children before visiting the hospital. They were reportedly dispensed by the local pharmacists on parents' demand even without any prescription from the registered practitioner. We noted that hospital travel was often challenging for parents owing to rugged hilly terrains, torrential rains, and limited transport facilities.

We also visited several health camps in the Kongpokpi district to understand the health needs of children. The health needs included proper food and nutrition, sanitation, safe drinking water, regular health check-ups, and other stationery items for school [2]. It was heartening to see the motivation of the community in maintaining hygiene, including the water supply and waste disposal, even though these were makeshift arrangements. Efforts by the district administration and several non-governmental organizations (NGOs) to help children resume education in local schools were noteworthy. Children in the relief camps presented with minor illnesses only. Most of them were well nourished, and only a few had clinical pallor.

To address these health needs, we conducted a one-day training session for integrated child development service (ICDS) workers with the support of the district administration. The primary goal of the training was to build community resources to manage minor health concerns, and protect persons against long travel and high expenses. The training session was attended by 24 ICDS workers, including Anganwadi workers and supervisors. Case-based discussions were held using the principles of adult learning. Topics included breastfeeding, complementary feeding, the use of integrated management of neonatal and childhood illness (IMNCI) protocols for the treatment of common ailments [3], including diarrhea, fever, ear pain, and cough, and management of eye flu. Emphasis was laid on identifying red flag signs for hospital referral and irrational use of antibiotics. A session on stress management and identification of symptoms of depression and anxiety followed this. The training session was lauded both by the participants, and the district administration.

As the dedicated efforts of the community, administration, and NGOs continue, the physical and mental health of children in the Kangpopki district is likely to improve. Moving through a humanitarian crisis is no easy feat, but children possess incredible resilience.

JAYA SHANKAR KAUSHIK,[1*] SHARAD PHILIP[2]

[1]Department of Pediatrics, All India Institute of Medical Sciences (AIIMS), Guwahati, Assam.

[2]Department of Psychiatry, AIIMS, Guwahati, Assam.

[*]jayashankarkaushik@gmail.com

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Variables Impacting Pain Perception With Various Heel Prick Devices in Neonates

We read with interest the article by Devi, et al. [1] in the *journal*. We appreciate the efforts of the authors in planning and executing this randomized controlled trial (RCT). However, we wish to highlight some observations concerning the study.

The authors stated that the outcome assessors and the statistician were blinded. However, upon reviewing the declaration of author contributions, it appears that the same author was involved in recruitment, data collection, and analysis. This situation could potentially compromise the blinding process and introduce bias.

While the study mentioned the use of an automatic lancet calibrated to puncture uniformly up to a preset depth of 1.5 mm, it remains unclear what depth of puncture was employed with the manual lancet or hypodermic needle for study purposes. Ensuring uniformity in the 'depth of puncture' among study participants is essential, as it can directly influence the perceived pain. Additionally, the methodology does not specify whether one or more personnel performed the intervention and whether they received prior training on aspects such as the depth and duration of the prick, the waiting time before squeezing, and the amount of pressure applied during the heel squeeze. Such details are crucial to ensure uniformity in the procedure, which could otherwise significantly impact the outcomes of interest.

The study employed video recording for assessment, including the duration of audible cry. However, it would be vital to know the position of the microphone in relation to the participants while recording, and whether efforts were made to maintain uniform background noise levels in the neonatal intensive care unit during interventions.

It is mentioned that study participants were fed at least one hour before the intervention. However, the way of feeding i.e., direct feeding, *paladai*, or tube feeds is not detailed. Breastmilk given orally through direct feeding or *paladai* has a greater analgesic effect than breastmilk given through tube feeds [2], which could potentially act as a confounding factor.

The perception of pain and the tendency to cry can be influenced by the Prechtl general behavioral state of the newborn. Infants in Prechtl states 1 and 2 (sleeping) during painful stimuli exhibit a reduced response to pain compared to awake babies [3]. Whether the study team ensured uniformity in the behavioral state of participants during interventions or pain assessment needs to be clarified.

The authors hypothesized that the pain score would be lower with the use of an automatic or manual lancet compared to a 26G hypodermic needle. However, there is substantial evidence supporting the superiority of automatic lancets over manual lancets [4,5]. Nonetheless, we commend the study team for meticulously conducting this complex RCT.

MAHESH VENKATACHARI,
THIRUNAVUKKARASU ARUN BABU*
Department of Pediatrics,
AIIMS, Mangalagiri, Andhra Pradesh.
**babuarun@yahoo.com*

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AUTHORS' REPLY

We thank the authors for their interest in our study [1]. Their comments have given us an opportunity to provide more details of our study, that could not be provided in the article [1].

The principal investigator (RD) recruited the patients. Another two authors (MP and SB) did the video analysis independently to measure the PIPP-R score and other variables. Both of them were blinded to the group allocation. This avoided the introduction of any potential bias.

The depth of manual lancet used was 3 mm (28G round lancet, Dr. Safe, Safe Lancet Engg Pvt Ltd.). However, the depth of 26G needle depends on the expertise of the person performing the procedure. To maintain uniformity, two nursing officers with over two years of working experience in our neonatal intensive care unit performed all the procedures. Both of them were specifically trained for this purpose before the commencement of the study.

Video and audio devices were fixed on a tripod at a

mentioned in our article [1], a developmentally supportive environment with reduced light and noise was ensured during the heel prick.

The mode of feeding was dependent on the clinical condition of the neonate. It is expected in a randomized controlled trial that these confounders would be uniformly distributed across the groups.

We draw the readers' attention to the fact that PIPP-R score incorporates behavioral state of the infant as one of its components. Appropriate weightage is given to account for the variability of behavioral states.

It is true that previous studies have documented automatic lancets to be better than manual lancets [2,3]; however, the automatic lancets used in these studies were of a different type, with a smaller puncture depth. The automatic lancet available in India and used in our study was of different type with larger puncture depth. We have already elaborated this point in the discussion section of the article [1].

SRIPARNA BASU
Department of Neonatology,
All India Institute of Medical Sciences,
Rishikesh, Uttarakhand.
sriparna.neonat@aiimsrishikesh.edu.in

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Tinea Nigra Palmaris

An 8-year-old boy presented with an asymptomatic hyperpigmented skin rash over the right palm for the last 2 months. Lesion started as a small dark spot and was slowly increasing in size. He had no history of preceding trauma, systemic disease, drug intake, or contact with exogenous chemicals. Physical examination revealed a single, irregularly shaped, well-circumscribed, brownish patch on the right hypothenar eminence (**Fig. 1**). There were no other mucocutaneous changes elsewhere. Short septate hyphae with budding yeast were found on skin scrapping and potassium hydroxide (KOH) mount. Dermoscopy revealed a light brown reticulate patch (**Fig. 2A**), formed by superficial fine thread-like, brown spicules that did not follow the dermatoglyphic furrows and ridges (**Fig. 2B**). Culture could not be done due to financialconstraints. Based on above findings, a clinical diagnosis of tinea nigra was made. Patient was treated with topical clotrimazole and after 4 weeks, the skin lesion resolved completely.

Tinea nigra is a superficial fungal infection caused by *Hortaea werneckii* [1]. It can occur in any age group but most often occurs in children and young adults [2]. It is typically seen in tropical climates, with excessive sweating being its major predisposing factor [1]. It presents as a hyperpigmented patch on the palms or soles and may be mistaken for acral nevus, silver nitrate stains, post-inflammatory hyperpigmentation, or acral lentiginous melanoma [2,3]. Acral naevus is smaller in size, darker in color and has linear striations while acral lentiginous melanoma more commonly occurs over soles, has indistinct borders and usually develops in patients aged over 60 years [4,5]. Negative history of preceding trauma or exposure to exogenous chemical helps rule out other differentials. Non-invasive tests like KOH mount and dermoscopic examination are helpful tools for the confirmation of the diagnosis and can help avoid unnecessary procedures like biopsy [1]. A limitation of our report is that culture, which remains diagnostic gold standard for fungal infection, was not done. Topical antifungals and topical keratolytics are the mainstay of therapy [3]. Complete resolution is usually achieved within two to four weeks of treatment [2].

DEVANSI SARAWGI,[1*] SUMIT SEN[2]
[1]Department of Dermatology,
Sri Balaji Vidyapeeth University, Puducherry.
[2]Department of Dermatology,
IPGMER-SSKM, Kolkata.
**devansi.sarawgi@gmail.com*

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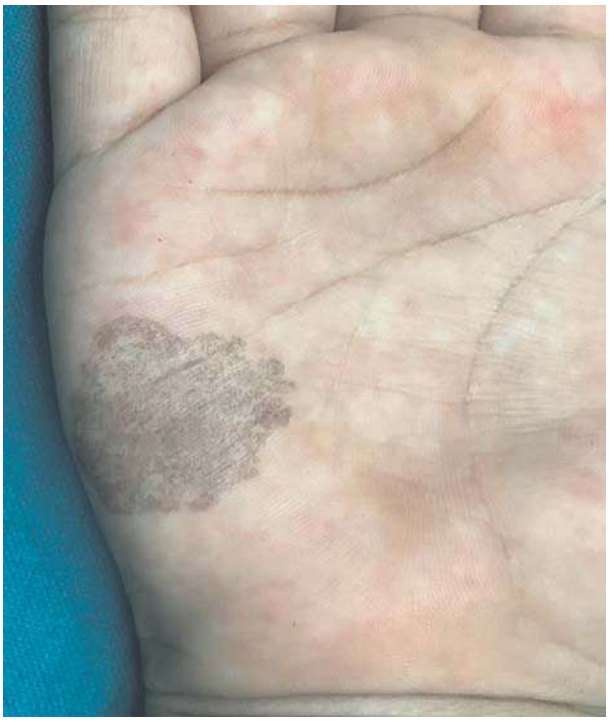
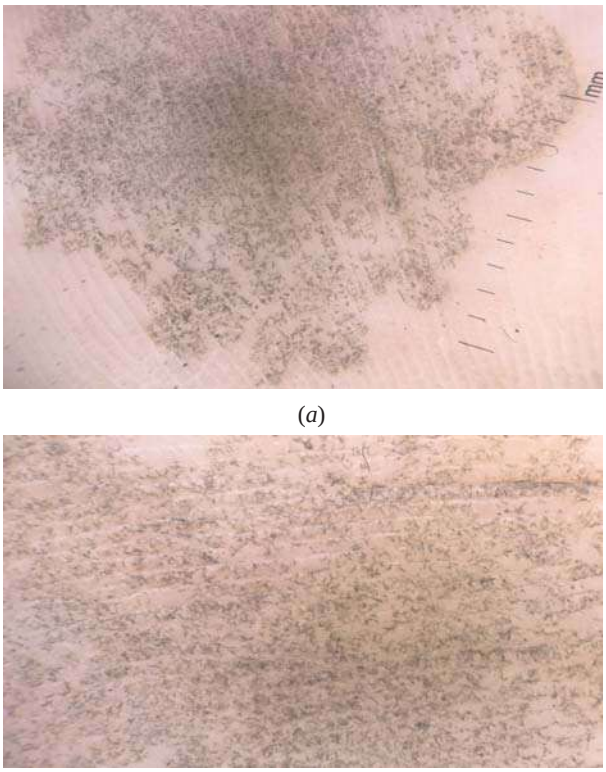


Fig. 1 Single, irregularly shaped, well-defined, brownish patch over the right hypothenar eminence in an 8-year-old child.

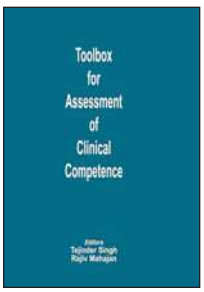


(*a*)

(*b*)

Fig. 2 Dermoscopy revealed *a*) light brown reticulate patch, *b*) formed by superficial fine thread-like, brown spicules that did not follow the skin lines.

BOOK REVIEW



Toolbox for Assessment of Clinical Competence
TEJINDER SINGH, RAJIV MAHAJAN
Pages: 136; Rs. 250/-

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The book has been designed as a manual or a ready referencer and starts with user instructions- just like any good manual- followed by a concise and comprehensive chapter on the principles of assessment. The manual is neatly organized in accordance with the Miller's pyramid: Assessment tools for Knows & Knows How, Shows and Does. Each tool is elucidated in a one dedicated chapter with a description of what it tests, the method itself, merits and demerits, possible modifications, and innovations. The list of references for further reading at the end of each chapter will hearten any teacher seeking in-depth understanding and clarity.

Sreenivas M
Director-Professor of Forensic Medicine,
University College of Medical Sciences, Delhi;
Hon. Faculty, RC-Department of Medical Education,
Maulana Azad Medical College, Delhi
drsreenivas.mamc@gmail.com

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