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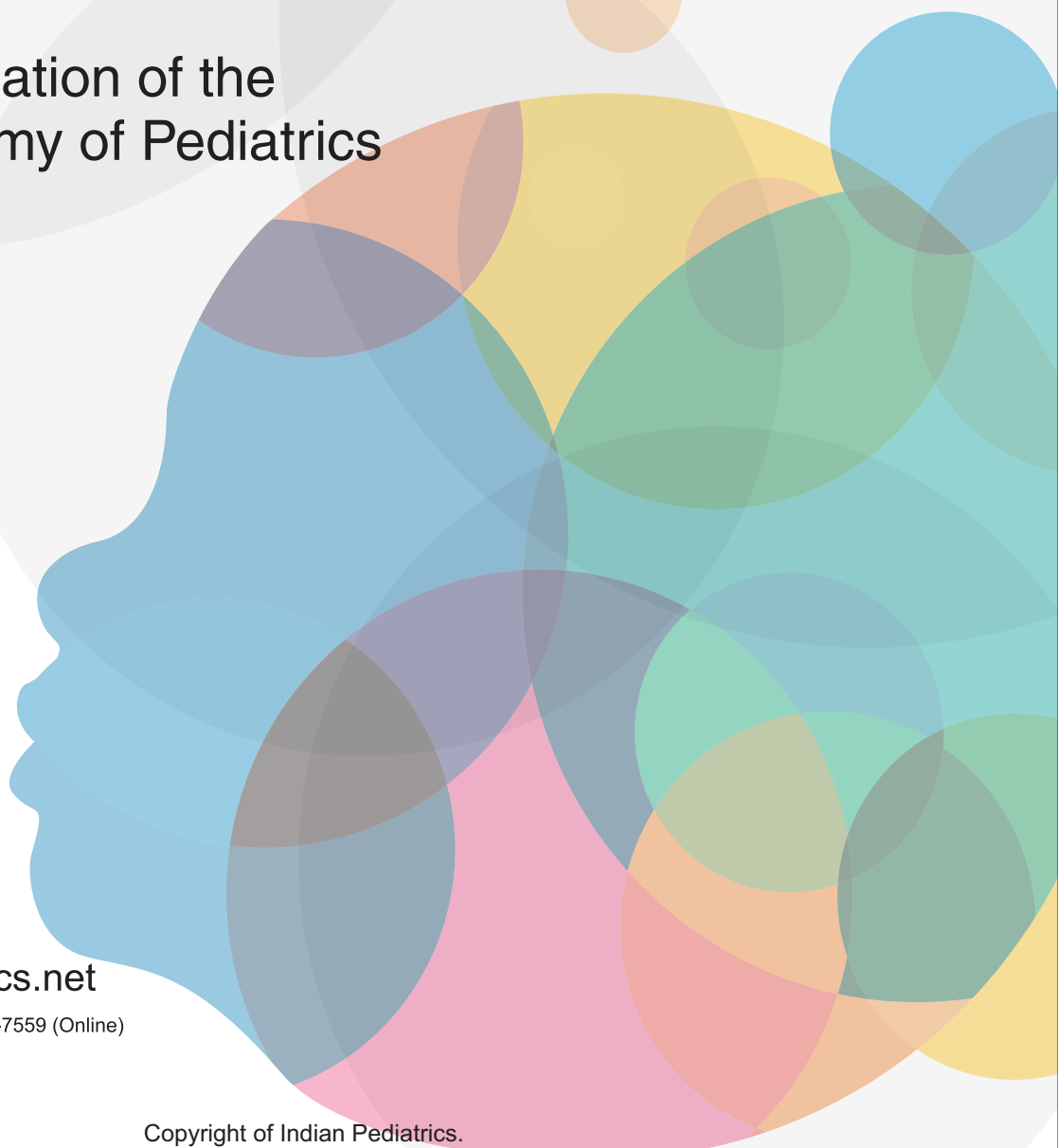

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PRESIDENTIAL ADDRESS

61st National Conference of the Indian Academy of Pediatrics (PEDICON) 25 January, 2024, Kochi, Kerala, India

GV BASAVARAJA
National President, Indian Academy of Pediatrics, 2024
president@iapindia.org

Dear Esteemed Members of the *Indian Academy of Pediatrics* (IAP),

I stand before you today with a heart brimming with gratitude and excitement as I outline our collective vision and plan for the remarkable year that lies ahead. As the National President of the *Indian Academy of Pediatrics* for 2024, I am honored and humbled by the trust you have placed in me. I am deeply grateful to the esteemed members of our Academy for their unwavering support.

Before I delve into my vision for the Academy for 2024, I want to express my heartfelt gratitude to the dedicated members of the new team who have not only embraced but also championed the vision that I am about to share. Your support is the bedrock upon which our aspirations stand, and I am truly fortunate to have such a committed team by my side.

My goals will be to achieve the 4 **As** which will be crucial to accomplish my vision for child health. These will include Academics, Advocacy, Administration and Accessibility.

Academics

Algorithmic Approach to Academics: We intend to implement a systematic algorithmic approach to further the academic training in pediatrics. By partnering with premier academic institutions, we will organize Training of Trainers (TOTs) with an aim to train the pediatricians and acquaint them with the recent guidelines and recommen-dations for managing the various health problems in children and also develop ready reckoners for practicing pediatricians.

Clinical Practice Guidelines: Developing evidence-based clinical practice guidelines addressing critical child health issues will be a part of the academic flagship activities. This will be aimed at ensuring uniformity in standards of care. A standardized protocol for the development, implementation, and dissemination of these guidelines will be established.

Thesis and Scientific Paper Writing Workshops: Conducting workshops all over the country on "Thesis and Scientific Paper Writing" to enhance the academic and research skills of residents and faculty members will enable us to contribute meaningfully to the academic mission of the organization.

Research Initiatives: We intend to foster more research initiatives to understand the unique needs of the diverse population, focusing on the prevalence, risk factors, and patterns of developmental and behavioral disorders in India. Utilizing the data so collected for tailored interventions and support services for our children will be the ultimate goal.

Advocacy

Liaison with Government for Health Policies: We will closely liaison with the Government to develop and formulate national health policies for children.

Public Awareness Campaigns and Policy Advocacy: It will be my endeavor to launch nationwide awareness campaigns advocating for policies that prioritize child health especially developmental and behavioral pediatrics. Integrating developmental screening into routine pediatric care will be a key advocacy goal for nurturing our children into productive adults.

Administration

Standard Operating Procedures: By establishing and implementing standard operating procedures (SOPs) for various processes within the organization, we will try to further streamline our functioning and ensure that the academic mission operates unhindered.

Inclusive IAP Community: Our mission will also be to make everyone responsible for the growth of the organi-zation by emphasizing inclusivity and unity. We intend to bring all the pediatricians under the umbrella of IAP in order to create a more inclusive and unified community, fostering collaboration and knowledge-sharing.

Collaboration for Training and Education: Collaborating with governmental bodies, non-profit organizations, and other stakeholders will enable us to create a comprehensive support system for enhanced training and education of pediatricians which will ultimately benefit the children. On this note, I am delighted to announce that the IAP and the University of Oxford have achieved a significant milestone in forming a collaborative partnership. The University of Oxford has agreed in principle to extend its Fellowship Program to our esteemed members, initiating a promising relationship.

Accessibility

Engagement with the community: Actively connecting with the community through "IAP ki Baat – Community ke Saath" will be an initiative directed towards making IAP an authentic center in disseminating information on child health to the masses and thereby making a meaningful impact at national level. This community engagement aligns with both advocacy and community health care activities.

Umbrella of IAP: We aim to bring together all pediatricians under the umbrella of IAP to create a more inclusive and unified community. This inclusive platform aims to amplify the impact, share insights, and collec-tively elevate the standards of pediatric care across the nation.

Emotional Essence of our Vision

This journey is not just about strategies and plans, it is also about emotions, shared dreams, and a commitment to achieve something larger than ourselves. It is about the tear in a parent's eye transformed into a smile through our collective efforts. It is also about the joy of a child's laughter echoing through the halls in every clinic guided by an IAP member.

Seeking Support for our New Journey

As we stand on the threshold of 2024, I invite each one of you to not merely witness this journey but to be an integral part of it. Your support is the heartbeat of our vision. Together, let us make 2024 a testament to the unity, compassion, and unwavering dedication that defines the Indian Academy of Pediatrics.

A Pledge for Unity and Compassion

Let our shared commitment be the guiding light that brings pediatricians from every corner of our vast nation under one umbrella. Let us stand united, shoulder to shoulder, as advocates for child health, as mentors to the new generation, and as beacons of hope for every family we touch.

As I close my address, let these words of gratitude and the call for unity resonate not just in our minds but also in our hearts. This is not just a new journey, it is an emotional odyssey, and I am honored to undertake it with each one of you. I sign off with profound gratitude and heartfelt anticipation.

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I, Dr Devendra Mishra, hereby declare that the particulars given above are true to the best of my knowledge and belief.

Sd/ Dr Devendra Mishra

Dated: February, 2024 Publisher

Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP): Recommended Immunization Schedule (2023) and Update on Immunization for Children Aged 0 Through 18 Years

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ABSTRACT

Justification: In view of new developments in vaccinology and the availability of new vaccines, there is a need to revise/review the existing immunization recommendations.

Process: The Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics (IAP) had a physical meeting on March 25, 2023, at Vaccicon, Kolkata, followed by online meetings to discuss the updates and new recommendations. Opinion of each member was sought on the various recommendations and updates, following which an evidence-based consensus was reached. The contents were finalized on September 8, 2023, during the National Conference of Pediatric - Infectious Diseases (NCPID) at Aurangabad. An online meeting of all members was held on November 15, 2023 and the recommendations were finalized.

Objectives: To review and revise the IAP immunization recommendations of 2020-21 and issue recommendations on existing and new vaccines.

Recommendations: The major changes include recommendation of HPV vaccine for boys; a 2-dose schedule of 9vHPV for boys and girls aged 9-14 y; a dose of Td vaccine at 16-18 y; guidance for injectable polio vaccine (IPV) for those patients who are changing from National Immunization Program to IAP schedule.

Keywords: *Boys, Guidelines, 9vHPV, Td vaccine*

Published online: *Jan 15, 2024*; **PII:** *S0974755916592*

The Advisory Committee on Vaccines and Immunization Practices of the Indian Academy of Pediatrics (IAP-ACVIP) met on March 25, 2023 in Kolkata, West Bengal, and September 8, 2023 at the National Conference of Pediatric - Infectious Diseases (NCPID), Aurangabad, Maharashtra. ACVIP members who attended the meeting are listed in *Annexure I*. The aim of the meeting was to discuss and debate the recent developments in the field of vaccinology, to issue the relevant recommendations based on them, and to revise the existing IAP immunization time-table. This document presents the consensus recommendations arrived at after detailed literature review, debates and discussions, held during the first physical meeting and subsequent meetings held online (dIAP or Zoom platform) and physically.

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PROCESS

The process for issuing recommendations included a review of the recent published literature including standard indexed journals, vaccine trials, recommen-

dations of reputed international bodies like Advisory Committee on Immunization Practices (ACVIP), Centre for Disease Control and Prevention (CDC), and World Health Organization (WHO) as well as unpublished data from vaccine manufacturers. Data generated by studies done in India was specifically looked at and available local information was given preference. The summary of the key updates of ACVIP 2023 recommendations is given in **Box I**.

RECOMMENDATIONS

The IAP-ACVIP recommendations for vaccine for routine use are presented in **Table I** and **Fig. 1**. The recommendations about the newly introduced vaccines are summarized in **Box II**.

1. Td (Tetanus, Diphtheria) Vaccine

Additional Dose of Td at 16-18 y

The National Immunisation Program (NIP) schedule recommends a Tetanus-Diphtheria (Td) booster at 16 years of age and the IAP-ACVIP schedule recommends a final booster of the Tetanus, Diphtheria, Pertussis (Tdap) vaccine at 10 years of age, followed by Td every 10 years [1,2].

Diphtheria surveillance data from Kerala (2016) found that the majority of the diphtheria cases were in the age group 18-45 y (38%; 198/526), followed by the age groups 10-18 y (31%; 161/526), and 5-10 y (18%) [3]. In north Maharashtra, the age groups of 5-9 y and 10-14 y represented 33.3% (42/126) and 23.8% (30/126) of the total diphtheria cases, respectively [4]. In a serosurvey done in 2,400 school children aged 6-17 y, studying in the various government schools in Hyderabad, only 56% and 64% had protective levels of IgG antibodies against diphtheria and tetanus respectively [5]. These studies suggest a lack of protective antibodies in a significant proportion of older adolescents and adults and a poor uptake of Td beyond 10 y of age.

Studies have demonstrated persistence of diphtheria antibodies in > 95% of adolescents at 5 y and 10 y following a Tdap dose at 10 y of age. Nearly all participants had tetanus antibodies (≥ 0.1 IU/mL) throughout the study, however, the protection against pertussis was variable. Anti-pertussis toxin antibodies declined to pre-vaccination levels approximately 5 y post-vaccination; antibodies to filamentous hemagglutinin, pertactin and fimbrae waned at 5 y and 10 y but remained several-fold higher than pre-vaccination levels [6,7]. A Tdap vaccine administered at 10-12 y will provide protection against tetanus and diphtheria for approximately 10 y [8]. These results support the recommendations that one Tdap booster should be administered to all persons and Td boosters every 10 y thereafter between 11-64 y of age.

Adolescents rarely visit the doctor unless they have a medical health condition. Estimates of receipt of clinical preventive services among adolescents, is suboptimal in developed countries [9] and very low in low- and middle-income countries. In a study done in rural West Bengal, it was reported that only 29.4% adolescents had utilised adolescent reproductive and sexual health services at least once during adolescence [10]. This may explain the poor uptake of adolescent boosters and the consequent higher incidence of diphtheria and tetanus in older adolescents and adults.

A booster of Td at 16-18 y will ensure assured protection against diphtheria and tetanus for the next 10 y. Replacement of the decennial Td by Tdap is not a cost-effective intervention [11], since the protective efficacy of Tdap administered in early adolescence, against pertussis does not last for more than 2-3 y. The reduction in pertussis disease burden attributable to the routine use of a second dose of Tdap would therefore be limited [12]. However, if there is an increased risk of pertussis in a healthcare setting evident by documented or suspected healthcare-associated transmission of pertussis, revaccination of healthcare personnel with Tdap may be considered [13].

IAP-ACVIP Recommendation

- The IAP-ACVIP recommends a dose of Td vaccine between 16-18 y.

Box I Key Updates and Major Changes in Recommendations for IAP Immunization Timetable 2023

Td Vaccine

- A dose of Td vaccine is recommended at 16-18 years.

Injectable Polio Vaccine (IPV)

- A child, who has received 3 doses of fIPV at 6w-14w-9 mo, does not need an additional dose of IM-IPV. However, the child should receive a 2nd booster of IM-IPV at 4-6 y

HPV vaccines

- HPV vaccines are recommended for boys
- For girls and boys 9-14 y, 9vHPV is recommended in a 2-dose schedule of 0-6 mo

New Vaccines

- Inactivated TZ84 strain of Hepatitis A vaccine marketed by BE Limited and Abott India Limited
- Quadrivalent HPV vaccine of Serum Institute of India Private Limited
- 14 valent pneumococcal conjugate vaccine of BE Limited
- MMR vaccine with Hoshino strain of Mumps of Zydus Lifesciences Limited
- Whole cell pertussis containing hexavalent vaccine of Serum Institute of India Private Limited
- Recombinant Zoster vaccine of GlaxoSmithKline

Table I IAP-ACVIP Immunization Timetable 2023: Vaccines for Routine Use

Age	*Vaccine*	*Comments*
Birth	BCG, OPV, Hepatitis B-1	BCG before discharge; OPV as soon as possible after birth; Hepatitis B should be administered within 24 hours of birth
6 wk	DTwP/DTaP-1, IPV-1, Hib-1, Hep B-2, Rotavirus-1, PCV-1	DTwP or DTaP may be administered in primary immunization; IPV: 6wk-10wk-14wk is the recommended schedule. If IPV, as part of a hexavalent combination vaccine, is unaffordable, the infant should be sent to a government facility for primary immunization as per UIP schedule.
10 wk	DTwP/DTaP-2, IPV-2, Hib-2, Hep B-3, Rotavirus-2, PCV-2	RV1 (GSK): 2 -dose schedule; all other rotavirus brands: 3-dose schedule
14 wk	DTwP/DTaP-3, IPV-3, Hib-3, Hep B-4, Rotavirus-3, PCV-3	An additional 4th dose of Hep B vaccine is safe and is permitted as a component of a combination vaccine
6 mo	Influenza (IIV)-1	Uniform dose of 0.5 mL ≥ 6 mo
7 mo	Influenza (IIV)-2	To be repeated every year, in pre-monsoon period, till 5 y of age
6-9 mo	Typhoid conjugate vaccine	There is no recommendation for a booster dose
9 mo	MMR-1	
12 mo	Hepatitis A vaccine	Single dose for live attenuated vaccine
15 mo	MMR-2, Varicella-1, PCV-Booster	
16-18 mo	DTwP/DTaP-B1, Hib-B1, IPV-B1	
18-19 mo	Hepatitis A-2, Varicella-2	Only for inactivated hepatitis A vaccine
4-6 y	DTwP/DTaP-B2, IPV-B2, MMR-3	
9-14 y	HPV	2 doses: 0-6 mo
10 y	Tdap	Tdap is to be administered even if it has been administered earlier (as DTP-B2)
15-18 y	HPV	3 doses; 0-2-6 mo (if not administered earlier)
16-18 y	Td	

Age in completed wk/mo/y. BCG: Bacillus calmette guerin; DTwP: Diphtheria, tetanus, and whole-cell pertussis; DTaP: Diphtheria, tetanus, and acellular pertussis; Hep B: Hepatitis B; Hib: Hemophilus influenzae B; MMR: Measles mumps rubella; OPV: Oral poliovirus vaccines; PCV: Pneumococcal conjugate vaccine; RVI: Monovalent rotavirus vaccine

2. Human Papilloma Virus (HPV) Vaccine

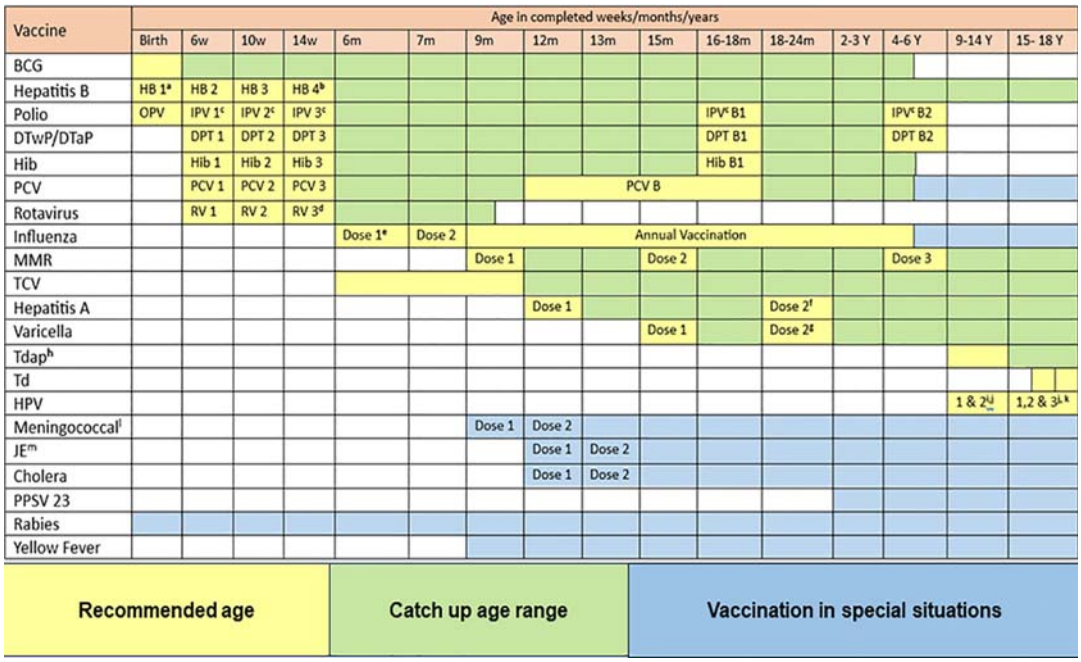
2-dose Recommendations for Girls and Boys Aged 9-14 y

All Human Papilloma Virus (HPV) vaccines were originally licensed and marketed using a 3-dose vaccination schedule. A 2-dose schedule was approved, based on demonstration of noninferiority of the immune response in the 9-14 y age group, when compared to young adult women in whom efficacy has been proven. A 2-dose schedule for 9-valent HPV *vaccine* (*9vHPV*) for 9-14 y was approved by USA CDC, European Medical Agency, Canada in 2016 and is currently approved in around 80 countries across the globe, including Australia, France, Germany, UK, USA as well as in Asian countries like, Singapore, Malaysia, Taiwan, Thailand and Vietnam.

9vHPV Vaccine Study: 2-dose Schedule Study

An open-label, noninferiority, immunogenicity trial was conducted to compare the seroconversion rates (SCR) and immunogenicity of 2 doses of 9vHPV in girls and boys aged 9-14 y as compared to 3 doses in adolescent girls and young women. Four weeks after the last dose, the SCR to each individual serotype, in the 2-dose cohort, was > 98%. The geometric mean titers (GMT) of HPV antibodies at 1 month after the last dose, for all the 9 HPV subtypes was higher in girls and boys who received 2 doses 6 months apart and in girls and boys who received 2 doses 12 months apart as compared with adolescent girls and young women who received 3 doses over 6 months. Noninferiority criteria for seroconversion rates were met for all 9 HPV types [14].

At follow up till 36 months, anti-HPV GMTs in girls and boys who received 2 doses were generally similar to or greater than GMTs in young women who had received 3 doses. Seropositive status was maintained across HPV types, in most boys and girls who received 2 doses and young women who received 3 doses till 2 to 2.5 y after the last dose [15]. In a follow up study of the 9vHPV vaccine, seropositivity rates remained > 90% through month 90 for each of the 9vHPV vaccine types. No cases of vaccine



a. To be given within 24 h after birth. When this is missed, it can be administered at first contact with health facility. All stable preterm and LBW babies should be administered a birth dose and 3 more doses with pentavalent/hexavalent combination vaccines.
b. An extra dose of Hepatitis B vaccine is permitted as part of a combination vaccine when use of this combination vaccine is necessary.
c. IPV can be given as part of a combination vaccine.
d. 3rd dose of Rota vaccine is not necessary for RV1 (GSK).
e. Influenza vaccine should be started after 6 months, 2 doses 4 weeks apart, usually in the pre-monsoon period. At other times of the year, the most recent available strain should be used. Annual influenza vaccination should be continued, for all, till 5 y of age. For those at high risk of Influenza related complications, annual vaccination should be continued till 18 years and beyond.
f. Single dose is to be given for the live attenuated Hepatitis A vaccine. The inactivated vaccine needs two doses.
g. 2nd dose of Varicella vaccine should be given 3-6 mo after dose 1. In catch up schedule, in those >12 years of age, the 2nd dose is to be given after 4 weeks.
h. Tdap should not be administered as the second booster of DPT at 4-6 y. For delayed 2nd booster, Tdap can be given after 7 y of age. A dose of Tdap is necessary at 10-12 y. If a dose of Tdap was administered at more than or equal to 9 y of age, the adolescent Tdap is not necessary. If Tdap is unavailable/unaffordable, it can be substituted with Td.
i. From 9-14 years, HPV vaccines are recommended as a 2-dose schedule, 6 months apart.
j. 9vHPV-Gardasil-9 is approved for boys between 9-14 years of age and females between 9-26 years of age. HPV4-SII is recommended for females and males between 9-26 years of age. Gardasil 4 is licensed till 45 years of age only for females.
k. From 15 y onwards and in immunocompromised subjects at all ages, HPV vaccines are recommended as a 3-dose schedule, 0-2-6 months.
l. Menactra is approved in a 2-dose schedule between 9-23 mo. Minimum interval between two doses should be 3 mo. Menveo is recommended as a single dose schedule after 2 y of age. For those with ongoing exposure to meningococci, boosters are recommended every 5 years.
m. In endemic areas.

Fig. 1 IAP-ACVIP Recommendations 2023

related high-grade intraepithelial neoplasia or genital warts were observed in the per-protocol population based on a maximum follow-up of 8.2 y (median 7.6 y) post-dose 3 [16].

Gender-neutral Vaccination: Need for HPV Vaccination for Males

Infection with the high-risk HPVs, principally serotype 16 and 18, is the cause of almost all cervical cancers in women. However, oropharyngeal cancer (including tonsils and base of tongue), anal and penile cancers are also HPV-associated cancers and impose a significant burden in males as well. It is estimated that HPV is the causal agent in 5% of all human cancers with HPV16 predominating. Apart from cervical cancers, the other HPV-associated cancers are not amenable to screening and are increasing in both males and females and usually detected at a late stage.

The aim of any vaccination program is to halt transmission of the pathogens and prevent all associated diseases. Gender neutral vaccination (GNV) will also prevent non-cervical HPV-associated diseases that have serious morbidity in males as well. GNV programs have been found to be cost-effective interventions [17]. GNV

Box II IAP-ACVIP Recommendations on Newer Vaccines

4vHPV: Cervavac

Schedule for Cervavac:

- 9-14 years of age (boys and girls): Two-dose schedule (0.5 mL at 0 and 6 months). The interval between the 1st and 2nd dose should not be <5 months.
- 15-26 years of age (females and males) and immunocompromised: 3-dose (0.5 mL at 0, 2, and 6 months) schedule. The second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose.

Inactivated TZ84 strain Hepatitis A vaccines: Hapibev and Havshield

- This vaccine is recommended for the prevention of Hepatitis A in children ≥ 12 months of age in a 2-dose schedule of 0-6 months.

14 valent pneumococcal conjugate vaccine of BE Limited: PneuBEvax 14

- This vaccine is recommended for the primary immunization, for the prevention of invasive pneumococcal disease caused by pneumococcal serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, in a 6w-10w-14w schedule. This vaccine is presently not recommended for the booster dose in the 2nd year of life.

MMR vaccine with Hoshino strain of Mumps: ZyvacMMR

- There is immunogenicity and safety data available in children between 15-18 months only, so this vaccine is recommended in children between 15-18 months.

Whole cell pertussis containing hexavalent vaccine: Hexasiil

- This vaccine is recommended for primary immunization against diphtheria, tetanus, pertussis, Hepatitis, Poliomyelitis and Hemophilus influenzae type B infections, in infants in a 6wk-10wk-14wk schedule.

Recombinant Zoster vaccine: Shingrix

- This vaccine is recommended in all immunocompetent adults aged ≥ 50 years, irrespective of prior receipt of varicella vaccine or zoster vaccine live (ZVL).

will reduce transmission, impart herd immunity, facilitate the eradication of HPV and protect boys from infection. Girls only vaccination programs will not lead to eradication.

Global/India Burden of Oropharyngeal Cancers (OPC)

Globally, head and neck cancers are the sixth most common cancer and one of the most common cancers in India [18]. The annual crude incidence rate per 100,000 in India has been reported as 2.4 in males and 0.52 in females. In India, in 2020, there were an estimated 17,175 new cases of OPC in males and 3,442 in females, with 10,367 deaths in males and 2,066 in females [19]. The contribution of HPV to squamous cell carcinoma of head and neck has been rising and presently stands at 47.7% overall and up to 72.2% in oropharyngeal cancers. As compared to HPV-negative head and neck cancers, HPV positive head and neck cancers tend to affect patients who are younger, consume less or no alcohol, and do not smoke. They are generally diagnosed at a higher stage and may have distant metastasis at diagnosis. They have a reasonably good response to the treatment [20].

A systematic review from India showed the prevalence of HPV in head and neck cancers ranging from 0-86.6% in India. The broad range resulted from the heterogeneity of the data. Data from 3,847 patients of head and neck cancer patients showed that 1,110 patients were HPV positive, implying a cumulative prevalence of HPV positive head and neck cancers in India around 28.85%. There was no difference in treatment outcome among HPV positive and HPV negative cancer patients [21].

Global/India Burden of Anal Cancers

HPV related cancers also include anal cancers with approximately 90% of anal cancers being related to HPV. In the meta-analysis study carried out by De Sanjoseì et al in 2019, HPV16 was present in 80.7% of anal cancers [22]. Worldwide, in 2020, there were an estimated 29,159 cases of anal cancer in women with an age-standardized rate (ASR) of 0.58/100,000 and 21,706 cases of anal cancer in men with an ASR of 0.49/100,000. There were an estimated 9,877 deaths in women and 9,416 deaths in men [23].

Estimated figures for India were, 3,111 cases in males and 2,341 in females, with an estimated 1,560 deaths in males and 1,216 deaths in females [19]. In a study done from two major cities in India, the prevalence of anal HPV was 95% (95% CI 91%-97%) in men who have sex with men (MSM) [24]. Among the women living with HIV from India, the anal HPV prevalence was 14.3% and high-risk HPV prevalence was 9.2% [23].

Global/India Burden of Penile Cancers

Worldwide, in 2020, there were an estimated 36,068 cases of penile cancers (PeCa), with 13,211 deaths [18]. The estimated burden in India was 10,677 cases and 4,760 deaths, with an estimated age-standardized incidence of 0.84 cases per 100 000 person-years (95% CI: 0.79-0.89) [19]. In a single centre analysis of 40 cases from India, the overall prevalence of HPV in PeCa was 42.5% as compared to 20% in controls. Among the subtypes, the most common subtype was HPV 16 noted in 33.3% of cases, followed by HPV 18 in 29.2% of cases [25].

HPV immunization in Male Population

Above mentioned data support the use of HPV vaccines in males. To date, 125 countries have introduced HPV vaccine in their national immunization program for girls, and 47 countries also recommend HPV vaccination for boys [26].

IAP-ACVIP Recommendation

- Due to the significant burden of HPV related cancers and other conditions, the IAP-ACVIP recommends the use of HPV vaccines in boys.
- All currently licensed HPV vaccines, including 9vHPV vaccines have excellent safety profiles and are highly efficacious, or have met immune bridging standards in both male and female. 9v HPV Vaccine is recommended in a 2-dose schedule with an interval of six months, for boys and girls between 9 to 14 y. This schedule also has cost-saving and programmatic advantages that may facilitate high coverage. The 3-dose schedule of the, 9vHPV vaccine is recommended for females, when the schedule is initiated after 15 years of age.

3. Injectable Polio Vaccine

Guidance on Changeover from NIP to IAP Schedule

The IAP-ACVIP, recommends five doses of full-dose (0.5 mL) intramuscular (IM) inactivated polio vaccine (IPV), including three primary doses at 6wk, 10wk and 14wk and two booster doses at 16-18 mo and 4-6 y [1]. The National Immunization Programme (NIP) recommends 3 doses of fractional-dose (0.1 mL) inactivated polio vaccine (fIPV) at 6 wk-14wk-9mo given intradermally (ID), along with bivalent oral polio vaccine (bOPV), 2 drops, at 6w-10w-14w and 16-18 mo [27].

It is not uncommon for a changeover from the NIP to the IAP schedule after 6 months of age as the NIP does not provide for many of the vaccines recommended by IAP for infants beyond 6 months of age. For this reason, guidance is being issued regarding use of IPV in children shifting from the NIP to the IAP schedule.

Following 2 doses of fIPV at 6wk-14wk, the IAP-ACVIP recommended an additional dose of full dose IM-IPV at least 8 wk after the last dose of fIPV [28]. This recommendation was made as 2 doses of fIPV at 6wk-14wk resulted in seroconversion of 82-85% against type 2. It was expected that an additional dose of IM-IPV will increase the seroconversion rates to a much higher level. The NIP now recommends 3 doses of fIPV at 6wk-14wk-9mo, with the 9 mo dose being a booster dose [27]. There is no substantial difference in seroconversion rates between 2 and 3 doses of ID fIPV, and 2 and 3 doses of full-dose IM-IPV, although the full dose gives higher titres of antibodies for poliovirus type 1, 2, and 3 [29].

A 2-dose schedule of IPV at 14w and 36w resulted in seroconversion rates of 96%, 98% and 85%, for serotypes 1, 2 and 3 respectively, by the intradermal route and 99%, 99% and 97% by the IM route [30]. Hence, any additional benefit from an additional dose of IM-IPV, will be of marginal benefit only. Two doses of fIPV administered at 14wk and 36wk resulted in higher seroconversion rates compared to an earlier schedule of 6wk and 14wk, for all serotypes: fIPV 96%, 98%, 85% (14 wk and 36 wk); 83%, 84%, 83% (6 wk and 14 wk) [30,31].

IAP-ACVIP Recommendations for IPV

- For infants who have received the 3-dose fIPV as per the NIP, an additional dose of IM-IPV is not necessary at 16-18 mo.
- A booster of IM-IPV is recommended at 4-6 y. The rationale for a booster at 4-6 y has been published earlier [1].

NEW VACCINES

The newly introduced vaccine products are detailed below and the IAP-ACVIP recommendations for these are given in **Box II**.

i) 9vHPV

The 9-valent HPV (9vHPV) vaccine contains serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58. Each 0.5-mL dose contains the L1 protein of~30 µg of HPV Type 6, ~40 µg of HPV Type 11, ~60 µg of HPV Type16, ~40 µg of HPV Type 18, ~20 µg of HPV Type 31, ~20 µg of HPV Type33, ~20 µg of HPV Type 45, ~20 µg of HPV Type 52, and ~20 µg of HPV Type 58. Each 0.5 mL dose of the vaccine also contains approximately 500 µg of aluminium (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 µg of polysorbate 80, 35 µg of sodium borate, <7 µg yeast protein, and water for injection. The product does not contain any preservative or antibiotics.

Route of administration: Intramuscular (IM)

Storage: The vaccine is stored between +2° to +8°C and should not be frozen. Any frozen vaccine should be discarded. The vaccine should be protected from light.

Clinical studies: The phase III efficacy trial consisted of a cohort of 14,000 females aged 16-26 y, in which the efficacy of 9vHPV was compared to 4vHPV for the prevention of ≥ CIN2, vulvar intraepithelial neoplasia (VIN) grade 2 or 3, and vaginal intraepithelial neoplasia (VaIN) grade 2 or 3 caused by HPV 31, 33, 45, 52, or 58 [32]. The results are shown in **Table II**. The immuno-

genicity of 9vHPV to 6, 11, 16 and 18 was noninferior to that of 4vHPV. This was used to infer efficacy of 9vHPV against 6, 11, 16 and 18. In the 9vHPV group, the GMTs of antibodies against 6, 11, 16 and 18 was noninferior to that of 4vHPV and >99% seroconverted against all 9 serotypes.

In an immune bridging trial comparing 9vHPV in 2,400 females and males aged 9-15 y with 400 females aged 16-26 y, > 99% seroconverted against all 9vHPV serotypes. The GMTs in the 9-15 y cohort was significantly higher than the 16-26 y cohort [14].

In a cohort of 600 adolescent females aged 9-15 y comparing 4vHPV and 9vHPV, the seroconversion rate (SCR) was 100% in both groups and the GMTs were noninferior in the 9HPV group as compared to the 4vHPV group. SCR was > 99% and GMTs were noninferior in males aged 16 through 26 y compared with females of the same age group [33].

Concomitant administration of 9vHPV with Tdap and the meningococcal conjugate vaccine did not interfere with the immunogenicity against all 9 HPV serotypes [32]. In the safety analysis, most adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity. The safety profiles were similar in 4vHPV and 9vHPV vaccines. Among females aged 9 through 26 y, the local reactogenicity with 9HPV was more than that observed with 4vHPV [32].

IAP-ACVIP Recommendations for 9vHPV

- Females and males aged 9-14 y: 2 doses at an interval of 6 to 12 months.
- Females 15-26 y: 3-dose schedule of 0-2mo-6mo
- 3-dose schedule in immunocompromised in both age groups.

ii) 4vHPV New

This new 4-valent HPV (4vHPV) vaccine is produced from *Hansenula polymorpha*. Each dose of 0.5 mL contains the L1 protein of HPV type 6 ≥ 20 µg, HPV type 11 ≥ 40 µg, HPV type 16 ≥ 40 µg, HPV type 18 L1 ≥ 20 µg, Al^{3+}≤ 1.25 mg.

Indications: In females 9-26 y of age for the prevention of the following diseases caused by HPV serotypes included in the vaccine: cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18, genital warts (condyloma acuminata) caused by HPV types 6 and 11, cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS), and CIN grade 1 caused by types 6, 11, 16, and 18, VaIN grades 2 and 3, VIN grades 2 and 3, and anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

In males 9-26 y of age for the prevention of the following diseases caused by HPV types included in the vaccine: Anal cancer caused by HPV types 16 and 18, genital warts (condyloma acuminata) caused by HPV types 6 and 11, AIN grades 1, 2, and 3 caused by 6, 11, 16, and 18.

Contraindications: Hypersensitivity to the active substances or to any of the excipients of the vaccine. Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of the vaccine.

Clinical studies: The phase 2/3 study, participants were divided in 2 cohorts. The cohort 1 consisted of 350 males and 349 females aged 9 to 14 y who received two doses of new 4vHPV vaccine six months apart and 338 females received the existing 4vHPV vaccine. Cohort 2 consisted of males and females age 15 to 26 y who received 3 doses in a 0-2mo-6mo schedule. In this cohort, 381 males and 411 females received the new 4vHPV vaccine and 378 females received the three doses of existing 4vHPV vaccine [34].

The primary objective of the study was to demonstrate immunogenic noninferiority of the new 4vHPV vaccine (Cervavac) to the existing 4vHPV (Gardasil-4), one month after the last dose i.e., at 7 months. In the cohorts of 9-14 years age, Geometric Mean Fold Rise (GMFR) for all 4 serotypes was > 1000-fold. In the same cohorts, noninferiority was demonstrated for high risk (oncogenic) HPV types as lower bound of GMT ratio (CI was above 0.5). Post-vaccination, at 7-month time point (1 month after the last dose), a 100% seroconversion was reported across all four vaccine types (serotypes 6, 11, 16, and 18)

Table II 9vHPV Vaccine Efficacy Data

Endpoint related serotypes	*Endpoint*	*VE (%)*	*(95% CI)*
HPV 31, 33, 45, 52, 58	≥ CIN2, VIN2/3, VaIN2/3	96.7	(80.9-99.8)
	≥ CIN2	96.3	(79.5- 99.8)
	6-month persistent infection	96.0	(94.4-97.2)

VE: Vaccine efficacy, HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia, VIN: Vulvar intraepithelial neoplasia, VaIN: Vaginal intraepithelial neoplasia; 9vHPV: 9-valent human papilloma virus

in initially seronegative populations. The GMT ratios observed between the new 4vHPV vaccine (Cervavac) to the existing 4vHPV (Gardasil-4), in 9-14 years age group are shown in **Table III** [34]. The new 4vHPV was found to be noninferior to the comparator vaccine in 15-26 years as well (unpublished data; Personal communication).

Safety profile: Most of the adverse effects reported were predominantly mild to moderate in intensity and recovered completely. No vaccine related SAE or solicited reactogenicity with severity of Grade 3 or more was reported. Overall incidence of AEs with the newer HPV was similar to that observed with the comparator vaccine.

Contraindications: Hypersensitivity to the active substances or to any of the excipients of the vaccine, including severe allergic reactions to yeast (a vaccine component) after a previous dose of the vaccine.

IAP-ACVIP Recommendations for the new 4vHPV

- IAP-ACVIP strongly recommends the use of HPV vaccines.
- 9-14 y of age (boys and girls): Two-dose schedule (0.5 mL at 0 and 6 mo). The interval between the 1st and 2nd dose should not be < 5 mo.
- 15-26 y of age (females and males): 3-dose (0.5 mL at 0-2 mo-6mo) schedule. The second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose.
- Not licensed beyond 26 y.

iii) Inactivated Hepatitis A vaccines: TZ84 strain

These vaccines are inactivated Hepatitis A vaccines derived from the TZ84 strain of Chinese origin. Healive (Sinovac) the original vaccine derived from the same strain, is a WHO prequalified vaccine. Vaccine bulk of Healive is imported and then fill-finished in Indian units to produce the vaccine.

Composition: Each 0.5ml dose which is in a pre-filled syringe contains: Inactivated HAV antigen (TZ84): 250 u, aluminium hydroxide: 0.175 ~ 0.31 mg qs, disodium hydrogen phosphate: qs, sodium chloride: 4.5 mg, sodium dihydrogen phosphate: qs, water for injection: qs to 0.5 ml [35]. It is produced in human diploid cells.

Storage: The vaccine should be stored at +2°C to + 8°C and should not be frozen. Vaccine, if frozen should be discarded.

Shelf life: 3 y

Dosage and schedule: The vaccine is to be administered in a 2-dose schedule. The 1st dose should be administered after 12 months of age and the second dose is to be given 6 months later (i.e., 0, 6 months schedule). The vaccine is for intramuscular injection.

Clinical phase 3 study in India: In a phase 3 study done in India, 2 doses of the TZ84 strain vaccine, with inactivated Hepatitis A vaccine (HM175 strain) vaccine, as a comparator, administered IM 6 months apart, in two age cohorts (1-7 and 8-15 y), resulted in 100% seroconversion at day 210 following vaccination in both the groups. 75.54% subjects in the TZ84 group and 73.93% in the inactivated Hepatitis A vaccine (HM175 strain) group achieved > 4-fold increase in anti-HAV IgG antibodies concentration at day 210 from baseline, which were similar. A similar trend was also observed for TZ84 vaccine and inactivated Hepatitis A vaccine (HM175 strain) groups in the age subsets of 1-7 y (85.47% vs. 82.46%) and 8-15 y (65.52% vs. 65.83%). The GMC of anti-HAV IgG antibodies (mIU/mL) at day 210 was significantly higher in the TZ84 vaccine group compared with the inactivated Hepatitis A vaccine (HM175 strain) [40139.65 (95% CI: 32889.82, 48987.55) vs 18167.84 (95% CI: 14451.70, 22839.550] [36]. Overall, 11.35% of recipients reported any adverse effects (AEs); 10.77% in the TZ84 vaccine group and 11.92% in the inactivated Hepatitis A vaccine (HM175 strain) group. The majority of AEs were mild in severity. Injection site pain was the most common AE (reported in > 5% of subjects) in both TZ84 strain vaccine and inactivated Hepatitis A vaccine (HM175 strain) groups. The majority of AEs (89/93; 95.70%) were reported within 7 days of vaccination [36].

Table III Comparison Between the new 4vHPV Vaccine and the Quadrivalent HPV Vaccine in 9-14 years of age

Serotype	*GMT ratio in Girls (98·75% CI)*	*GMT ratio in Boys (98·75% CI)*
HPV 6	0·95 (0·83-1·08)	0·90 (0·78-1·03)
HPV11	0·69 (0·61-0·78)	0·62 (0·54-0·71)
HPV 16	0·88 (0·76-1·01)	0·76 (0·65-0·88)
HPV 18	1·26 (1·09-1·46)	1·05 (0·91-1·22)

IAP-ACVIP Recommendations on New Inactivated Hepatitis A Vaccines

- These vaccines derived from TZ84 strain are recommended in children aged ≥ 12 mo, in a 2-dose schedule of 0-6mo.

iv) 14-valent Pneumococcal Polysaccharide Conjugate Vaccine

Composition: Each dose of 0.5 mL of this vaccine contains 3 µg *Pneumococcal* polysaccharide serotype 1, 2.2 µg each of *Pneumococcal* polysaccharide serotypes 3, 4, 5,

7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, and 4.4 µg of *Pneumococcal* polysaccharide serotype 6B. It is adsorbed onto aluminium phosphate. The polysaccharides are conjugated to 20-50 µg of CRM197 [37].

Indications: It is indicated for the prevention of invasive pneumococcal disease caused by pneumococcal serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F from 6 weeks of age onwards.

Schedule: Primary immunization in a 6w-10w-14w schedule.

Contraindications: Known hypersensitivity to previous dose of vaccine or known hypersensitivity to any component of the vaccine.

Storage: At +2°C - +8°C. The vaccine should not be frozen. Any frozen vaccine should be discarded.

Clinical studies: A single blind randomized active-controlled phase 3 study to evaluate immunogenicity, safety, and tolerability of BE's 14-valent pneumococcal polysaccharide conjugate vaccine was administered to 6-8-week-old healthy Indian infants in a 3-dose (6 wk-10 wk-14 wk) primary dosing schedule, 0.5 mL per dose, intramuscularly. The comparator vaccine was PCV-13. A total of 1290 (645 in test vaccine arm, 645 in comparator arm) infants were enrolled from 15 sites across India. The primary end point was to demonstrate noninferiority of BE-PCV14 to PCV-13 in terms of proportion of subjects seroconverted (anti-PnCPS IgG titres ≥ 0.35 µg/mL) for the 12 common serotypes at day 86. BE-PCV 14 demonstrated noninferiority with PCV 13 with respect to proportion of subjects who seroconverted with anti-PnCPS IgG titres ≥ 0.35 µg/mL, on day 86 for the 12 common serotypes (unpublished data taken from product insert) [37].

For serotypes 22F and 33F (which are not part of PCV-13) seroconversion rate of the BE-PCV-14 group were compared with the lowest performing serotype in the PCV-13 group (ie, serotype 3). Comparison of the GMC titers and GMC ratios between BE-PCV-14 and PCV-13, showed was noninferiority of BE-PCV-14 to PCV-13 for all shared serotypes and against 2 unique serotypes (22F and 33F). Comparison of opsonophagocytosis assay (OPA) (proportion of subjects with OPA ≥ 1:8 lower limit of quantitation) and OPA GMT, showed was noninferiority of BE-PCV-14 to PCV-13 for all the 12 shared serotypes. The proportion of subjects with OPA ≥ 1:8, was 98.2% for ST 22F and 96.5% for ST 33F. 27% of subjects in the BE-PCV-14 group and 28% of subjects in the PCV 13 group showed adverse effects. In a safety and immunogenicity study in 12-23 months toddlers (phase 2), the SCR in the BE-PCV-14 group, were noninferior to the PCV 13 group [37].

IAP-ACVIP Recommendations on 14v Pneumococcal Polysaccharide Conjugate Vaccine

- IAP/ACVIP recommends the 14v Pneumococcal Polysaccharide Conjugate Vaccine for the prevention of invasive pneumococcal disease caused by pneumococcal serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, in a 6wk-10wk-14wk schedule.
- This vaccine is presently not recommended for the booster dose in the 2nd year of life due to lack of adequate data.

v) Whole cell Pertussis (wP) containing Hexavalent Vaccine

This is a fully liquid vaccine which contains diphtheria and tetanus toxoids, pertussis (whole cell), hepatitis B (rDNA), poliomyelitis (inactivated) and Hemophilus influenzae type B conjugate vaccine.

Each 0.5 ml dose of this vaccine contains: diphtheria toxoid: ≥ 30 IU, tetanus toxoid: ≥ 40 IU, B. pertussis (whole cell): ≥ 4 IU, HBsAg (rDNA): 15 µg, Inactivated polio vaccine (Salk): Type 1: 40 DU, Type 2:8 DU, Type 3:32 DU, Hib PRP: 10 µg, conjugated to TT: 19-33 µg, Aluminium Phosphate ≤ 1.25 mg and 2-Phenoxyethanol 0.5%.

Indications: For the active immunization of infants beyond six weeks of age against diphtheria, tetanus pertussis, hepatitis B, poliomyelitis and invasive disease caused by *Hemophilus influenzae* type B. It is recommended for primary immunization, in a three-dose scheduled at 6wk-10 wk-14 wk.

Contraindications: Moderate to severe hypersensitivity reaction occurring after the previous administration of any dose of DPT containing vaccines. It is also contraindicated in those with known hypersensitivity to any of the vaccine constituents. It is also contraindicated in infants who developed an acute encephalopathy of unknown etiology, within seven days of previous administration of DPT containing vaccine. Infants with a progressive neurological illness or uncontrolled seizures should not receive this vaccine. Acute moderate to severe illnesses are a precaution for administration of this vaccine [38].

Clinical study: In a noninferiority phase 3 clinical trial, wP containing hexavalent vaccine was compared to simultaneously administered wP containing pentavalent vaccine and Injectable Polio vaccine of the same manufacturer. The noninferiority criteria for all antigens were ~10%. The GMC for all antigens in infants, were comparable and establishing the noninferiority of the new wP containing hexavalent vaccine compared to wP

containing pentavalent vaccine and Injectable Polio vaccine of the same manufacturer. No significant difference was reported in the incidence of local and systemic AEs [Unpublished data].

A phase 2 study done in toddlers to compare the safety, reactogenicity and immunogenicity of the new wP containing hexavalent vaccine compared to wP containing pentavalent vaccine and Injectable Polio vaccine of the same manufacturer administered simultaneously, showed non-inferiority in seroconversion rates [Unpublished data].

IAP-ACVIP Recommendations on wP Containing Hexavalent Vaccine

- This vaccine is recommended for primary immunization against diphtheria, tetanus, pertussis, hepatitis, poliomyelitis and *Hemophilus influenzae* type B infections, in infants in a 6wk-10wk-14wk schedule. Sufficient data is not available regarding the use of this vaccine as a booster dose in the second year of life. IAP/ACVIP does not recommend this vaccine as a booster in the second year of life.

vi) Measles Mumps and Rubella (MMR) Vaccine Containing Hoshino Strain of Mumps

This is a live attenuated vaccine which consists of Edmonston Zagreb strain of measles virus propagated in human diploid cells, Hoshino strain of mumps virus propagated in chick fibroblast cells and RA27/3 strain of rubella virus propagated in human diploid cells. This is a freeze-dried vaccine (0.5 mL) vial, which comes with sterile water for injection, and is to be reconstituted before use [39].

Strength: Each dose of 0.5 mL of this vaccine contains not less than 1000 CCID50 live attenuated measles virus (*Edmonston zagreb* strain) propagated on human diploid cells, 5000 CCID50 live attenuated mumps virus (*Hoshino* Strain) propagated on chick fibroblast cells and 1000 CCID50 live attenuated rubella virus (RA27/3 Strain) propagated on human diploid cells.

Clinical indication: Indicated for active immunization against measles, mumps and rubella.

Contraindications: Subjects with moderate to severe allergic reaction to previous dose of the vaccine or known hypersensitivity to any other component of the vaccine, pregnancy. Pregnancy should be avoided for 1 month following vaccination, Moderate to severe immunosuppression due to drugs, radiation, advanced leukemia or lymphoma, serious malignant disease or some congenital disorders of immunity.

Clinical studies: The phase 2 study was done in 123 healthy children 15-18 months of age, who were administered a single dose of the Hoshino strain Measles Mumps and Rubella (MMR) vaccine from either the single-dose or the multi-dose formulations. The SCR for anti-measles and anti-mumps antibodies was 100% while that for anti-rubella antibodies was 98.9% after the MMR vaccination. Even in those seropositive prior to vaccination, SCR were 100% for measles and mumps and 99.1% for rubella. The GMT of anti-measles, anti-mumps and anti-rubella antibodies was 3154.0 mIU/mL, 90.6 EU/mL and 141.7 IU/mL, respectively. The vaccine was well tolerated, with 21.8% reporting some adverse event. The most common adverse event reported during the study was fever in 19 subjects (15.4%) followed by rash and rhinorrhea in five subjects (4.1%) each [40].

The phase III clinical trial, conducted on 328 children of either sex, aged 15-18 months, was a noninferiority trial with the existing Indian MMR vaccine as the comparator vaccine. The seropositivity rates for measles was 100.0% in both groups, 94.5% vs. 94.0% for mumps and 95.5% vs. 91.0% for rubella [41].

Among the subjects seronegative at baseline, the seroconversion rates for the test vaccine and the comparator vaccine were 100.0% & 100% for measles, 94.0% & 93.3% for mumps, and 95.1% & 91.5% for rubella. The GMT for anti- measles antibodies at the end of the study was significantly greater in the test vaccine group (2355.5 mIU/mL) than in the comparator group (1448.1 mIU/mL) ($P < 0.01$). There was no difference in the adverse event profile of the two groups ($P > 0.05$). Most of the adverse effects were classified as "mild' in intensity [41].

The results of this phase III clinical trial show that the test vaccine was noninferior to the comparator MMR vaccine and both had comparable, mild adverse effects profile.

IAP-ACVIP Recommendations on Hoshino Strain MMR Vaccine

- Since the phase 2 and 3 trials for this vaccine were done in children in age range of 15-18 months, there is immunogenicity or safety data available only in this age group. IAP/ACVIP recommends this vaccine to be used in children 15 -18 months of age.

vii) Recombinant Zoster Vaccine

The recombinant zoster vaccine (RZV) contains the gE antigen of the Varicella Zoster Virus (VZV), which is obtained by culturing genetically engineered Chinese Hamster Ovary cells, which carry a truncated gE gene, in media containing amino acids, with no albumin, antibiotics, or animal-derived proteins. The gE protein is purified by several chromatographic steps, formulated

with excipients, filled into vials, and lyophilized.

Composition: Each 0.5-mL dose contains: 50 µg of the r-gE antigen, 50 µg of MPL and 50 µg of QS-21. The vaccine does not contain any preservative [42].

Storage: The vaccine should be stored at +2°to +8°C, protected from light and should be discarded if frozen. After reconstitution, the vaccine should be administered immediately or stored refrigerated between 2° and 8°C (36° and 46°F) for up to 6 hours prior to use.

Schedule: *The* schedule consists of 2 doses; the first dose is followed by the 2nd dose, 2-6 month later, by IM route.

Contraindications: Hypersensitivity to the active substances or to any of the excipients.

This can be administered simultaneously with unadjuvanted inactivated seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPV23) or Tdap. The vaccines should be administered at different injection sites [42].

Clinical Phase 3 studies: The ZOE-50 study was done in adults > 50 y. In this study, the overall vaccine efficacy (VE), in those > 50 y was 97.2% (95% CI, 93.7 to 99.0; *P* < 0.001), with similar VE in age groups 50-59 y, 60-69 y and > 70 y [43,44]. The ZOE-70 study was done in adults >70 y. In this study, the overall VE observed was 89.8% (84.2-93.7), with VE of 90.0% (83.5-94.4) in 70-79 y and 89.1% (74.6-96.2) in those > 80 y. The VE at the end of the 1st year was 97% (88.8-99.7) with a sustained VE of 85.1% (64.4-94.9) at the end of 4 y [45]. The VE against post-herpetic neuralgia (PHN) was 88.8% (68.7-97.1) in adults > 70 y and 91.2% (75.9-97.7) in those > 50 y. When the data of ZOE 50 & 70 were pooled, overall, VE was 91.3% (86.8 to 94.5), with similar VE in the 70-79 and > 80 y age groups. The pooled VE against PHN was 88.8% (68.7 to 97.1) in those > 70 y and 91.2% (75.9 to 97.7) in those > 50 y [46]. In the long term follow up study over 10 y, the overall VE from 1 month post-dose 2 was 89.0% (85.6-91.3). At the end of year 1 it was 97.7% (93.1-99.5), at year 6, 88.5% (74.9-95.6) and year 10, 73.2% (46.9-87.6) [47].

Efficacy of this vaccine in the immunocompromised has also been studied. In patients who had undergone an autologous bone marrow transplant, the overall VE was 68.2% (55.5-77.9). In the 18-49 y age group, the VE was 71.8% (38.7-88.3) and in those > 50 y, 67.3% (52.6-77.9). VE against PHN was 89.3% (95% CI: [22.5; 99.8]). In adults with hematological malignancies, the VE was 87.2% (95% CI: 44.3-98.6) [48].

Good humoral and cell mediated immunity (CMI) has been demonstrated in subjects with solid tumours, recipients of solid organ transplant, HIV, rheumatoid arthritis, inflammatory bowel disease, other acquired immunodeficiencies and chronic medical conditions.

All solicited reports of injection-site reactions including grade 3, and of systemic reactions including grade 3 were much higher in the vaccine group as compared to the placebo. However, the rate of all serious adverse events, potential immune-mediated diseases and death were similar in the vaccine and placebo groups.

In USA, in 2017, the vaccine was approved for adults > 50 y [49] and in 2021, for those > 18 y, who are or will be at increased risk of Herpes Zoster due to immuno-deficiency or immunosuppression caused by known disease or therapy [50].

IAP-ACVIP Recommendations on Recombinant Zoster Vaccine (RZV)

- ACVIP recommends the recombinant Zoster vaccine, to all immunocompetent adults aged ≥ 50 y, irrespective of prior receipt of varicella vaccine or zoster vaccine live (ZVL).
- It should be administered intramuscularly in a 2-dose schedule, with the 2nd dose administered 2-6 months after the first dose.
- If the 2nd dose is administered at an interval of < 4 weeks, it is an invalid dose and should be repeated at least 4 weeks after the early dose.
- For those who have received ZVL, RZV may be offered at least 2 months after the ZVL dose.
- RZV is recommended to those with past history of HZ. It may be administered any time after clinical recovery.
- Presently, in India, this vaccine is not recommended for individuals before 50 y of age.

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ANNEXURE I

Members who attended the physical meeting in Kolkata (March 25, 2023): Indra Shekhar Rao, Srinivas G Kasi, Arun Wadhwa, B Rajsekhar, Rajendra Khadke, Sanjay Lalwani, Bhaskar Shenoy, Ananda Kesavan TM, Srinivas Kalyani, Chandra Mohan Kumar, Kripasindhu Chatterjee, Vineet Saxena, Upendra Kinjawadekar, Basavaraja GV. Shashi Kant Dhir could not attend the meeting.

Members who attended the physical meeting in Aurangabad: Indra Shekhar Rao, Srinivas G Kasi, Shashi Kant Dhir, B Rajsekhar, Rajendra Khadke, Sanjay Lalwani, Bhaskar Shenoy, Ananda Kesavan TM, Srinivas Kalyani, Chandra Mohan Kumar, Kripasindhu Chatterjee, Vineet Saxena, Upendra Kinjawadekar, Basavaraja GV. Arun Wadhwa could not attend the meeting.

INVITED COMMENTARY

Continuous Glucose Monitoring and Dietary Assessment Unveils Challenges and Opportunities in School Age Children With Type 1 Diabetes in the School and at Home

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Care for children with type 1 diabetes (T1D) is challenging, and poverty, low literacy and poor awareness further complicate disease management in countries with limited resources. The majority of T1D cases in youth are diagnosed during the school years when the child is still dependent on caregivers and other adults for daily needs. The use of continuous glucose monitors (CGM) improves diabetes management in multiple ways. In this issue of *Indian Pediatrics*, Singh and colleagues report the dietary intake and glycemic patterns on blinded CGM among a small series of school-age (4-19 years) Indian children with T1D (n = 22) over a single sensor session [1]. Compared to diabetes care and outcomes in other countries, Indian children face unique challenges, including poor community awareness, social stigmatization, and cost considerations which limit access to glargine insulin, insulin pumps, and glucose monitoring equipment. Nevertheless, mean hemoglobin (Hb) A1c in this cohort was 7.7%, similar to the median HbA1c in a recent report from the international SWEET registry [2] and lower than the mean HbA1c of 8.4% in the T1DX-QI registry in the United States [3]. On face value, these Indian pediatric patients' diabetes management appears favorable.

However, despite the overall glycemia measured by HbA1c, CGM revealed notable trends that may be generalizable across a large portion of school-attending students with T1D in India. During the school day, hyperglycemia (CGM glucose > 180 mg/dL for > 15 minutes) was noted on three quarters of the days and accounted for nearly 60% of the time at school. The authors note that multiple cultural factors lead to this pattern, including parental fear of hypoglycemia at school, nondisclosure of the child's diabetes to school personnel, and the fact that very few Indian children are able to receive a prandial insulin dose at the 11 AM snack at school [4].

Without a shift in social acceptance of T1D, this pattern of hyperglycemia is very hard to address. Adults caring for children with diabetes at school should be aware of the potential for immediately treatable dangerous medical situations; care should involve a collaboration between the parents and the school personnel, and the children themselves should be progressively introduced to developmentally-appropriate self-care strategies that will slowly prepare them to transition to successful diabetes management as adults. This patient-centered approach has been successfully adopted elsewhere, such as the United States [5].

The researchers importantly note that improving access to CGM could improve diabetes management at school by reducing the fear of hypoglycemia. Notwithstanding access, social acceptability will also be an important factor in CGM uptake. Another area for improvement may be macronutrient optimization in the breakfast and the 11 AM snack, which the authors note will require further study. This could be done independently of the above steps and may be more immediately practical.

Contrary to daytime hyperglycemia, subjects' overnight pattern was characterized prominently by hypoglycemia (CGM glucose < 70 mg/dL) occurring on 45% of nights, with 20% of time spent in hypoglycemia. Nocturnal hypoglycemia in children is of particular concern because most events are asymptomatic [6]. Although nighttime only accounts for a portion of the day, 20% time in hypoglycemia is relatively large, far greater than the full-day upper limit recommendation for time in hypoglycemia of 4% by the International Society for Pediatric and Adolescent Diabetes [7] and twice the time spent < 70 mg/dL than was seen in a large pediatric trial from the United States [8]. This should raise concern that school-age children with diabetes in India may be at relatively higher

risk of severe hypoglycemia than many of their counterparts in other countries. Again, widespread CGM access and uptake could help mitigate this risk.

Also notable, such large periods spent in hypoglycemia likely counterbalance daytime hyperglycemia's effect on raising HbA1c. The causative role of glycemic variability in the development of micro- and macro-vascular complications is unclear in pediatric T1D, but evidence of a link with adults with type 2 diabetes may encourage clinicians to emphasize time in range as a clinical target, if it is not already a more practical day-to-day focus for people living with diabetes than the longer-term HbA1c [9].

Although CGM remains an out of reach technology for many children in the developing world, this study points us toward some practical considerations that could potentially improve glycemia in this population. The researchers found that carbohydrates accounted for 62% and 68% of calories at the dinner meal when families included or did not include dal, respectively. Dal is a protein-rich lentil, common in the diet in this region. In both scenarios, this proportion of carbohydrate intake is higher than what is recommended by the Indian Council of Medical Research, which recommends 50-60% of total calories come from carbohydrate and 15-25% be from protein [10]. Dinners without dal were associated with higher risk of overnight hypoglycemia. Therefore, similar to breakfast, adjusting macronutrient intake in the dinner to include dal or other foods, such as nuts, soya granules/chunks, egg, chicken, fish, and meat, all with comparatively more protein than the dal, may potentially reduce the risk of nocturnal hypoglycemia.

It should also be highlighted that not one child in this study administered insulin with the 11 AM snack, a function of local practice and the cultural barriers. In a large, multinational pediatric T1D study, teaching patients to receive insulin for all snacks was the only nutrition education practice studied that was associated with a greater proportion of the population meeting recommended HbA1c goals [11].

In summary, this study of Indian children with T1D demonstrates a variety of potential opportunities to improve diabetes management. Some challenges will be very difficult to address; overcoming social barriers will take time, and increased access to CGM will require financial solutions. However, optimizing nutrition may be a realistically achievable goal for the short-term management, one that may be most quickly accepted by clinicians, families, and schools.

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ORIGINAL ARTICLE

School-time Hyperglycemia and Prolonged Night-Time Hypoglycemia on Continuous Glucose Monitoring in Children With Type 1 Diabetes

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ABSTRACT

Objective: To document glycemic patterns during school and sleep by continuous glucose monitoring system (CGMS) in school-going children with type 1 diabetes. To correlate glycemia with meal composition.

Methods: Patients with type 1 diabetes (n = 22) aged 4 to 19 years were enrolled. Food recording was taught, and a retrospective CGMS sensor was worn by them for 6 to 14 days. Dietary composition and glycemic patterns during school and sleep were analyzed.

Results: The mean (SD) of dietary carbohydrate was 62.9 (9.2)% of daily calories (high) and protein 13 (2.5)% (low). Sensor glucose > 180 mg/dL (hyperglycemia) was detected on 73% of 139 school day CGMS records and involved 58 % of the school time. Sensor glucose < 70 mg/dL (hypoglycemia) was present on 45% of 172 nights. Time below range was 20 (25)%. Mean (SD) protein content (g) of dinner was significantly higher when it included lentil (*dal)* than without [20.4 (9.7) vs 15.3 (8.3); P < 0.001]. Hypoglycemia occurred less often on nights with vs without *dal* for dinner (42.1% vs 51.7%; P = 0.048).

Conclusions: Hyperglycemia during school hours was notable. The inclusion of lentil (*dal)* in the night meal in the traditional diet may reduce nocturnal hypoglycemia.

Keywords: *Blood glucose, Diet, Legumes*

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INTRODUCTION

Indian children with type 1 diabetes mellitus (T1D) face unique challenges while trying to achieve a good glycemic control. Poor general awareness about childhood diabetes leading to social stigmatization is one among them [1]. Consequently, the diagnosis of T1D is often not disclosed in school. Insulin doses before mid-school snacks are not acceptable to the majority of children with T1D in our region [2]. Further, many parents are concerned about hypoglycemia during school and try to mitigate this risk by providing a large breakfast. These concepts are only anecdotal beliefs among diabetes management team experts, and scientifically recorded blood glucose (BG) data during school hours are lacking.

In contrast, nocturnal hypoglycemia in T1D is well documented in international literature. Continuous glucose monitoring (CGM) technology revealed that nocturnal hypoglycemic episodes were frequent, prolonged, and largely asymptomatic [3,4]. Hypoglycemia during sleep can be reduced with dietary intervention [5]. Dinner is invariably abundant in carbohydrates and is usually eaten between 8 to 9 PM in this region. A protein-rich dinner/bedtime snack may protect against late-night hypoglycemia due to the glycemic profile of delayed generation of BG from protein and fat [5-7]. *Dal* (lentil) is an important source of protein as well as complex carbohydrates of low glycemic index, and a staple food in this region. However, it is traditionally often a part of lunch rather than the night meal, the latter often including only cereals and vegetables (or occasionally mutton, chicken or boiled egg curry in a non-vegetarian family or cottage cheese/paneer curry). The effect of *dal* on protection from nocturnal hypoglycemia has not been documented previously.

This CGM-based study was conducted to assess the glycemic patterns in children and adolescents with T1D during the daytime in school and at night. The dietary profile of these children was also evaluated with respect to breakfast and mid-morning snack, as well as dinner and bedtime snack, seeking associations of glycemic patterns with dietary composition.

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METHODS

This prospective cohort study was conducted over a period of one-year, between July 2020 and August 2021, in the pediatric diabetes clinic of our institute. The sample size was a sample of convenience. Consecutive children and adolescents aged 4 to 19 years with T1D who were being followed up for more than a year were invited to participate, provided either the participant or a parent had completed eighth grade or higher in school education. The family was required to live close to our city (for study logistics and better follow-up) and for the children and adolescents to attend school regularly.

Children with chronic microvascular complications of diabetes and other autoimmune comorbidities (celiac disease, hypothyroidism and Addison disease) were excluded. Continuous glucose monitoring system (CGMS) and diet (weighing, measuring, and recording of food) were explained to the eligible participants and their parents. After three days, they were evaluated for their willingness and ability to keep a good dietary record. Calibrated digital weighing scales were also provided to the families for weighing food. Approval from the institutional ethics committee was obtained before the study. Participants were recruited after obtaining a written informed consent from their parents.

The school hours of the study participants were from 8 AM to 2 PM. Children had breakfast before leaving for school, took a home-made snack at the 11 AM break, and lunch at 2.30 to 3.30 PM after they returned from school. Dinner was usually served between 8 PM and 9 PM and was invariably rich in carbohydrate. It is a routine instruction in our clinic to include one of the day's milk servings for the child at bedtime, so as to provide a protein-fat rich snack to prevent late night hypoglycemia. The Nutritional Value of Indian Foods as recommended by the National Institute of Nutrition, Hyderabad, was used as reference for dietary analysis [8]. Bedtime snacks were included in the dinner calculation if they were consumed within 120 minutes of dinner.

The sensors for CGMS used were from Medtronic i-Pro2 system with the Enlite sensor (Medtronic, Minimed), and Abbott Libre Pro system with its sensor (Abbott). i-Pro2 sensor was inserted on the anterior abdominal subcutaneous tissues for up to six days. The Libre Pro sensor was worn on the back of the arm for 14 days. For home blood glucose testing, the majority of patients used an Abbott Freestyle (Abbott) glucometer.

The following CGMS variables were documented *a*) episodes of elevated sensor glucose (SG > 180 mg/dL for 15 min) during school hours, usually 8 AM to 2 PM, *b*) time (h) spent with elevated SG during school hours, *c*) area under the curve of elevated SG during school hours (AUC_{school}), *d*) number of episodes of low SG (> 15 minutes with sensor glucose < 70 mg/dL) during sleep, *e*) time (hours) spent with low SG during sleep, *f*) area under the curve (AUC_{sleep}) below 70 mg/dL during sleep. AUC_{school} and AUC_{sleep} were calculated by the trapezoid method, taking the base every 5 min for Enlite sensor wear periods and 15 min for Libre sensor periods, the height being the maximum sensor glucose excursion in that interval. The method of reporting sensor glucose derived metrics has been previously described [9].

The team discussed the CGMS and diet record's analysis. The exercise diary was examined to see how it affected glycemic variability. Specific areas that needed to be improved were identified. Each family received a customized powerpoint presentation as well as a written report.

Statistical analysis: The Student t test was used to compare means of two groups, and Mann-Whitney U test was used to compare medians. Chi-square test was used to compare categorical variables. Correlation was assessed with Spearman test. Stepwise linear regression analysis (standardized coefficient beta–β) was performed with school time hyperglycemia as a dependant variable and the dietary parameters as independent variables. *P* value < 0.05 was considered statistically significant.

RESULTS

A total of 44 children were eligible; 22 children agreed to participate, and 18 children (61% boys) completed the study. The children who declined to participate in this study (*n* = 22; 11 boys) had a similar mean (standard deviation, SD) age (years) and HbA1c levels (%) as those who completed the study [12.6 (3.4) vs 12.9 (3.2), and 7.9 (1.0) vs 7.7 (1.1), respectively]; but had a longer disease duration than the participants [5.3 (2.6) vs 3.5 (2.5) years, *P* = 0.03]. The most common reason for refusal to participate was difficulty in keeping diet records.

Fourteen patients were on glargine for their basal insulin requirement, and four took twice-daily neutral protamine Hagedorn (NPH) insulin due to cost considerations. All patients used regular insulin everyday before breakfast, lunch, and dinner. No child was willing to take insulin before the school snack. Participants played usual informal games but no child recorded formal sport during the study period.

The macronutrient distribution of the meals for the entire day comprised a high mean (SD) carbohydrate proportion of 62.9 (9.2)% of daily calories, and a low mean (SD) protein proportion of 13.0 (2.5)%. Breakfast contributed 23.5 (9.6)% of the day's calories, mid-school

Table I Macronutrient Composition of Night Meals With or Without Lentil (*Dal)*

Dinner composition	*Dinner with dal (n = 114)*	*Dinner without dal (n = 58)*	*P value*
Total calories (Cal)	490 (401-661)	427 (342-635)	0.21
Carbohydrates (g)	84 (65-100)	67 (52-100)	0.32
Protein (g)	19 (14-24)	13 (9.6-19.6)	< 0.001
Fat (g)	8.2 (4.0-17.0)	12.2 (6.3-15.8)	0.78

Data represented as median (IQR). n represents the number of dinners evaluated among the 18 patients.

snack 14.3 (7.8)%, lunch 24.6 (7.8)%, evening snack 12.8 (6.3)% and dinner 29.7 (8.3)%. **Table I** shows the macronutrient distribution in dinner as per intake of *dal*.

Glycemia was evaluated by CGMS on 139 days and 172 nights. Hyperglycemia was documented on 73% of the 139 cumulative school days with a median (inter-quartile range, IQR) duration of 3.5 (2.5-6.0) hours (58.3% of school time) spent with high sensor glucose (**Web Fig. 1**).

Participants experienced nocturnal hypoglycemia on 45.1% (77/172) of cumulative night records, 42.1 % on the nights with dal for dinner vs 51.7% on the nights without dal for dinner, $P = 0.048$. Time below range (TBR) was 20%. A trend towards less nocturnal hypoglycemia was observed in other CGM metrics during nights when dinner included *dal* (**Table II**). Hypoglycemia prevalence was not different on the 81 nights when milk was taken after dinner, than that in the remaining 91 nights. A typical night time hypoglycemia pattern can be seen in a CGMS overlay shown in **Web Fig. 2**. No dietary parameter at dinner correlated with either time spent in hypoglycemia or AUC_{sleep}.

AUC_{school} and time spent in hyperglycemia in school hours correlated positively with total calories consumed in breakfast (r = 0.44 and 0.48 respectively, $P < 0.001$), carbohydrate content (g) of breakfast ($r = 0.41$ and 0.46, $P < 0.001$), protein content (g) of breakfast ($r = 0.44$ and 0.45, $P < 0.001$) and fat (g) content of breakfast ($r = 0.39$ and 0.37, $P < 0.001$). There was a weaker correlation between school-hours spent in hyperglycemia and school snack variables (with carbohydrates $r = 0.26$, $P = 0.019$; with protein $r = 0.22$, $P = 0.047$). Breakfast carbohydrates (B 0.353, $P < 0.001$) and breakfast fat (B 0.233, $P = 0.006$) predicted AUC_{school} as well as school-time spent in hyperglycemia.

Table II Nocturnal Glycemic Indices From Continuous Glucose Monitoring System With Respect to Consumption of Lentil (*Dal)*

Variables	*Night meal with dal (n = 114)*	*Night meal without dal (n = 58)*	*P value*
Nights with low sensor glucose (%)	0 (0-46.4)	19.6 (0 -78.6)	0.06
Time spent with low sensor glucose (h)	0 (0-3.3)	1.4 (0-5.5)	0.06
AUC_{sleep} below 70 mg/dL (mg/dL× h)	0 (0 -3.7)	0.7 (0-5.9)	0.09

Data shown as median (interquartile range). AUC: Area under the curve

DISCUSSION

This study showed prolonged and frequent hyperglycemia during the school day and hypoglycemia during the night in a small sample of children and adolescents with T1D in our region. Lower hypoglycemia episodes occurred at nights with *dal* than nights without *dal* for dinner.

In our study, students spent 58% of their school time with elevated SG. This could be due to the observed consumption of a large breakfast which is driven by a fear of hypoglycemia during school hours when the child is not under the direct observation of parents. The diabetes team is usually unable to optimize the morning dose of prandial insulin due to a lack of post-breakfast capillary BG testing opportunities. The mid-school snacks were not covered by an insulin dose, that may have contributed to high SG during late school hours. This can be addressed by access to real-time CGMS that alleviates fear of hypoglycemia, self-motivation and parents' willingness to allow injection in the school, and better school support for diabetes management [10,11]. The association between school time hyperglycemia and the composition of the school snack remains to be confirmed in larger studies, ideally with dietary intervention strategies.

There are few studies that have analysed glycemia particularly during school hours. A recent study from a developed country with greater resources for diabetes management in school showed a mean (SD) time-in-range (TIR) during school hours as 51 (23)%, against a recommended 70% or greater. They documented lower TIR in the early school hours as compared to later hours suggesting inadequate insulin dosing before breakfast to avoid hypoglycemia [12]. While not aimed at documenting glycemia during school, the only multicenter Indian study on the care of diabetes in school that enrolled 397 participants from 7 urban diabetes centres reported insulin administration in 47% at school [10]. This practice was associated with higher parental education, chiefly of the mother. The authors reported that schools were more often supportive (private more than government schools) for diabetes care activities than not.

Nocturnal hypoglycemia has been revealed with the use of CGMS in T1D earlier [3,4]. This was more frequent

WHAT THIS STUDY ADDS?

- Prolonged hyperglycemia during school and nocturnal hypoglycemia were documented.
- Low lentil intake in the night meal of a vegetarian diet was associated with nocturnal hypoglycemia.

(78% had hypoglycemia on at least one of the three nights of sensor use) and prolonged (median duration of hypoglycemia 3.3 hours) with asymptomatic nocturnal hypoglycemia in 91%, in a study of 28 children with T1D [3]. A significant association of nocturnal hypoglycemia with bedtime blood glucose was found [4]. Diabetes management has come a long way since then with technological advances [14]. Real-time CGMS is now available as a valuable tool to monitor and reduce hyper and hypoglycemia [13, 14]. The target for TBR using real time CGMS is less than 4% though the TBR in our study was as high as 20%.

The presence of *dal* in the night meal increased the protein content of the dinner and reduced nocturnal glycemia. Our study also highlighted the typical dietary pattern of children and adolescents with T1D in Uttar Pradesh. Their meal pattern reported disproportionately high carbohydrates (63%) against a recommended 50 to 55%) and low protein (13%) against a recommended 15 to 25% [13].

Our study has some limitations. Both the i-Pro2 and the Libre Pro CGMS systems were used; their accuracy and features are different from each other. The glycemic excursion (AUC) for the post-breakfast versus post-school snack periods was not calculated separately. An analysis for a more severe grade of hypoglycemia, below 54 mg/dL was not performed.

To conclude, this pilot observational study showed that school-time diabetes management is overlooked in our practice. There is a scope for improved dietary education to children and families with T1D to limit the glycemic variability.

Ethical clearance: Institutional ethics committee; No. 2020-147-DM-Exp-21, dated July 15, 2020.
Contributors: MS: Data collection and analysis, manuscript preparation; ZH: Data collection, analysis and manuscript review; PD: Data analysis and manuscript review; VB: Conceptualized the study, data analysis, manuscript preparation. All authors approved the final version of the manuscript and take responsibility for the data. VB will be the guarantor of the study.
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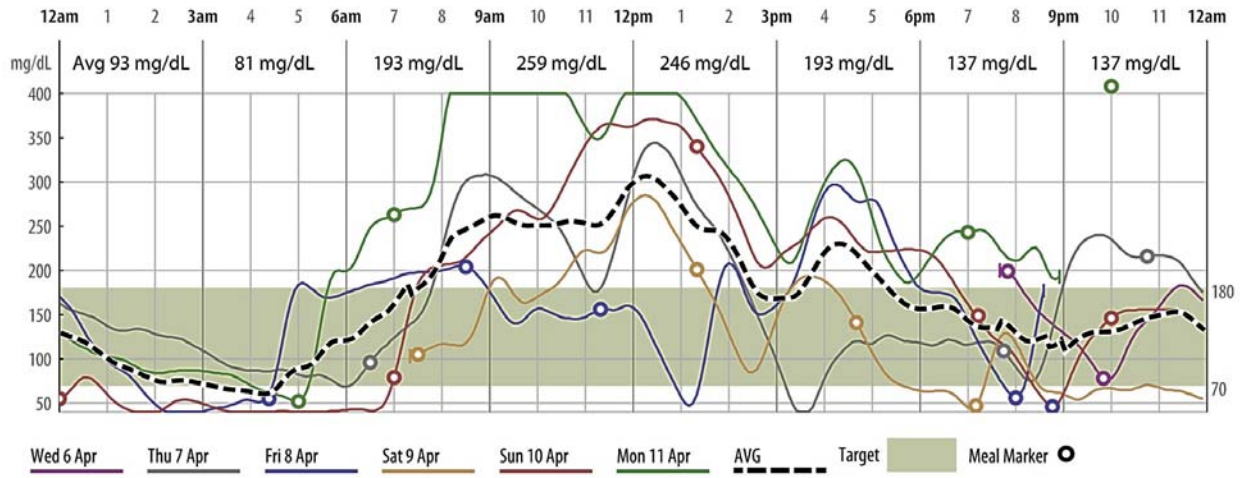
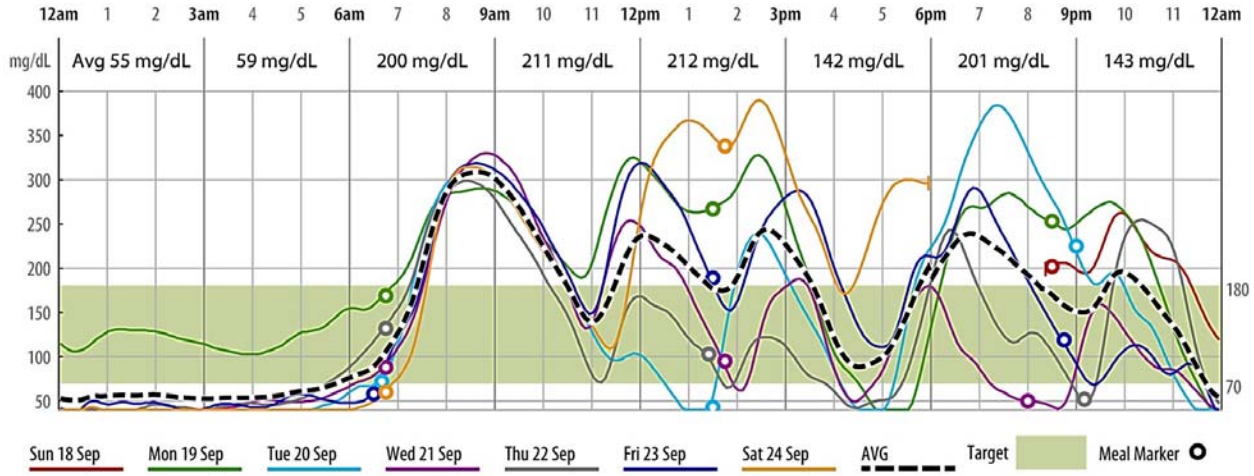


The sensor glucose overlay of a patient from our study reveals significant hyperglycemia during school hours. The time of day is represented on the X axis, and the sensor glucose level on the Y axis. The sensor glucose levels are represented by each color-coded line for a specific day.The average sensor glucose is depicted by the bold broken line. The shaded band between 70 and 180 mg/dL is the desirable level for sensor glucose. The average sensor glucose for each 3 hour period is also depicted in figures.

Web Fig. 1 School time hyperglycemia



A patient's sensor glucose overlay shows prolonged continuous nocturnal hypoglycemia on six of seven nights. The spike in sensor glucose levels after breakfast is also evident.The time of day is represented on the X axis, and the sensor glucose level on the Y axis. The sensor glucose levels are represented by each color-coded line for a specific day. The average sensor glucose is depicted by the bold broken line. The shaded band between 70 and 180 mg/dL is the desirable level for sensor glucose.

Web Fig. 2 Nocturnal hypoglycemia

ORIGINAL ARTICLE

Heparin vs Saline Infusion to Maintain Patency of Arterial Catheters in Children: A Randomized, Double-Blind, Noninferiority Trial

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ABSTRACT

Objective: To determine whether normal saline flush solution is noninferior to heparinised saline for maintaining the patency of arterial intravascular catheters in children

Methods: A single centre, double blind, parallel group, noninferiority, randomized control study was conducted in the Pediatric Intensive Care Unit of Kanchi Kamakoti CHILDS Trust hospital, a tertiary children's hospital, Chennai, India**.** 92 children requiring arterial catheters for more than 12 hours were randomized to receive either normal saline or heparinized saline (1 U/ml) flush solution. Primary outcome was a noninferiority comparison between normal saline and heparinised saline in maintaining the patency of arterial catheters using the proportion of occlusion of arterial catheters as primary endpoint. Secondary outcome was mean duration of patency of arterial catheters in each treatment group

Results: Ninety-two children with a median (interquartile range, age of 84 (33.5-132) months and 52% males were enrolled. 15.2% of catheters in the heparin group and 17.4% of catheters in the normal saline group were occluded (P = 0.77). The 95% upper confidence interval for the difference in proportion was 0.148 (+14.8%), establishing noninferiority (< 15%). The median (IQR) duration of a patent arterial catheter was 47 (27.75 - 94.5) hours in the heparin group and 35.50 (24.50 - 62) hours in the normal saline group (P = 0.10). Comparison of duration of patency using Kaplan Meier survival analysis and log rank test showed no statistically significant difference. There were no serious adverse events noted in either group.

Conclusion: Our data suggests that normal saline is noninferior to heparinized saline infusion in maintaining the patency of arterial lines in children. This may benefit clinicians worldwide as normal saline would be a safer and cost-effective option.

Keywords: *Indwelling, Occlusion, Sodium chloride, Thrombosis, Vascular patency*

Trial registration: Clinical Trials Registry of India (CTRI/2021/05/033438)

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INTRODUCTION

Invasive arterial cannulation enables accurate and continuous monitoring of blood pressure and facilitates regular blood sampling for various investigations in critically ill patients [1-4]. In Pediatric Intensive Care Units (PICUs), it eliminates the need for repeated venous and arterial punctures in young children, thus reducing the physical and psychological trauma associated with it. There are several factors which determine the patency and functional longevity of an arterial catheter. Some of them are the site of insertion, insertion technique, material of the catheter, volume and type of flush solutions used and the amount of external pressure applied to the flush solution [5,6].

The patency of arterial catheters is by and large maintained with a continuous pressurized flow of solution containing heparin to prevent clotting and occlusion [1,2,7]. Flush solutions containing anticoagulants like heparin and citrate might prevent the thrombus formation at the tip of the catheter [4,8]. However, there is lack of evidence to substantiate the role of either pressurized flush system or anticoagulant containing flush solutions in the prevention of thrombosis and catheter occlusion, especially in paediatric population [9]. There is also no consensus regarding the contents of the irrigating solution (heparinized or non-heparinized). In addition, there is huge variation in the volume and concentration of heparinized solutions administered [1,2]. Heparin flushes are associated with bleeding, albeit the risk is small. It may rarely lead to an immunological phenomenon called

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heparin induced thrombocytopenia and thrombosis, a dose-independent, potentially fatal complication of heparin exposure in which heparin-induced anti-platelet antibodies can cause thrombocytopenia and an increased risk of venous and arterial thrombosis [8,10].

Several recent adult studies and systematic reviews have shown non-heparinized solutions to be equally effective as heparinized solutions in maintaining arterial line patency [1,2,11,12]. Use of non-heparinized solutions may be preferable and beneficial considering the risks involved in using heparin. This is also beneficial in resource limited countries. In light of the sparse and inconsistent studies in the pediatric population, further research is pivotal to assess the use of non-heparinized solutions such as normal saline in maintaining arterial catheter patency.

We hypothesized that normal saline would be non-inferior to heparinized saline infusion in maintaining patency of arterial intravascular catheters in children and therefore, conducted a study to compare normal saline infusion to heparinized saline infusion in maintaining the patency of arterial intravascular catheters in children.

METHODS

The study was designed as a double-blind, randomized controlled, parallel group, noninferiority trial and was conducted in the PICU of Kanchi Kamakoti CHILDS Trust Hospital (KKCTH), a tertiary pediatric teaching and referral hospital in Chennai, India over a 6-month period from July, 2021 to December, 2021. The trial was registered with the Clinical Trials Registry of India (CTRI/2021/05/033438).

The PICU is a large 21-bedded facility catering to approximately 700 admissions per year in all medical and surgical specialities such as trauma, burns, general surgery, oncology, bone marrow transplant, neurology and neurosurgery, metabolic and endocrine medicine, infectious diseases, renal, spinal surgery, ENT, respiratory, cardiac and ECMO (extracorporeal membrane oxygenation) support. Children of either sex, aged 1 month to 18 years undergoing peripheral arterial catheterization were included in the study after obtaining caretaker's written informed consent. Children were included if the peripheral arterial catheter was kept for more than 12 hours after insertion. Children with known bleeding or coagulation disorder, hypersensitivity to heparin, being treated with anticoagulant or fibrinolytic medications, platelet count less than 100,000/mm^3 and children transferred from other hospitals with peripheral arterial catheter in place were excluded from the study.

Randomization was performed according to the Consolidated Standards for the Reporting of Trials (CONSORT) guidelines. Children were randomized to receive either normal saline infusion or heparinised saline infusion (Heparin 1U/mL) by a computer-generated randomization sequence. The details of this randomization sequence were held by the clinical pharmacist of the hospital and were concealed from both the investigator and the nursing staff. For the purpose of blinding, syringes were supplied with labels as either 'A' or 'B'. Contents of the syringe A or B were added to a 500 mL normal saline bottle to make a flush solution. The normal saline bottle with the added contents of the syringe was then mounted onto a pressure bag and pressurized to 300 mmHg which was connected via a transducer to the peripheral arterial line. The transducer was levelled to the phlebostatic axis and the system was calibrated to atmospheric pressure. The rate of infusion was set as 3 mL/hr for both solutions.

Demographic data, type of admission (medical/surgical), diagnosis, date and time of the arterial catheterization, site of the catheterization, number of attempts at catheterization, reason for arterial catheterization, platelet counts and coagulation profile nearest to the time of insertion along with adverse events were recorded for each participant. Trained doctors under ultrasound guidance inserted the arterial catheters. All catheters were 2.5cm, 22G polyurethane lines (Becton Dickinson India Private Ltd.). Pressure monitoring set with transducer (TruWave PX260, Edwards Life Sciences Private Ltd.) was connected to a patient monitor (Philips IntelliVue MX550). Functionality of the arterial catheter was defined by presence of patency, ability to draw back blood using a syringe, acceptable waveform on the monitor and appropriate response to fast flush. The arterial catheter was considered non-functional (occluded) if any of the above characteristics were lost. Functionality of the arterial catheter was evaluated immediately after the insertion and thereafter at eight hourly intervals. Assessment was also done when the arterial catheter was accessed for blood sampling or any manipulations like flushing the catheter or mobilization or when the arterial pressure waveform was abnormal on the patient bedside monitor. Tubing was regularly checked for the presence of blood clots and air bubbles. The transducer was accurately levelled to phlebostatic axis and zeroed at eight hourly intervals.

In the absence of backflow of blood or loss of acceptable waveform, nursing staff performed necessary manipulations like appropriate positioning of the limb, lavage of the arterial catheter using the flush solution to clear any clots or stasis of blood and cleared the tubing of any air bubbles. Functionality of the catheter was rechecked after the above manipulations. If the arterial catheter was still non-functional, it was considered as

'occlusion' and the catheter was removed. Data collection was continued until catheter removal and the reason for removal was noted in the data collection sheet. The rate of occlusion of arterial catheters in each treatment group along with the duration of patency were calculated. All bedside nurses and doctors in PICU were educated on the study purpose, protocol, data collection, handling the catheter and how to identify loss of patency.

Primary outcome was a noninferiority comparison between normal saline and heparinised saline in maintaining the patency of arterial catheters using the proportion of non-patency (occlusion) of arterial catheters in each treatment group as primary endpoint. Secondary outcome was median duration of patency of arterial catheters in each treatment group

Sample size estimation: Sample size was calculated assuming 8% rate of occlusion in both heparin and normal saline groups; using previous adult studies as reference [2,13-16]. For a significance level (alpha α) = 0.05, statistical power (1-beta β) = 80% and a noninferiority margin of 15% with an allocation ratio of 1:1 between the study groups, a total of 82 participants were required with 41 in each group. Assuming an attrition rate of 10%, the final sample size was calculated to be 92 participants [17]. A noninferiority margin of 15% absolute difference in the rates of occlusion of arterial catheters between normal saline and heparinized saline flush solution was chosen based on the expected rate of occlusion with heparinized saline from the previous studies and identifying a clinically meaningful difference between the study groups.

Statistical analysis: All the data were entered in a Microsoft Excel spread sheet. A descriptive analysis was performed using percentages for categorical variables and median with inter-quartile range (IQR) for continuous variables. Chi-square test was used for categorical variables, and the Student's *t* test for continuous variables. The median duration of the catheters was evaluated using the Kaplan–Meier method at removal. These results were presented graphically for both groups, and the groups were compared using the log-rank test. In all analysis, $P < 0.05$ was considered significant. All outcome analyses were performed according to intention-to-treat principle. All statistical analyses were performed using SPSS statistical software, version 20

RESULTS

A total of 214 children with peripheral arterial catheterization were screened during the study period, of which 122 were excluded as they did not meet the inclusion criteria (**Fig. 1**). Study participants were randomized to two groups Group A (heparinized saline, 1 U/mL) and Group B (normal saline). Group A was the control group and Group B was considered the intervention group for statistical analysis. The demographic characteristics of the 92 included study participants are described in **Table I**. The duration of catheter days ranged from 1-5 days. Patency assessments were documented for all catheters.

The demographic characteristics were similar between the study groups A and B. Overall, 93.5 % of the children were admitted due to medical conditions. The most common reason for arterial catheterization was for hemodynamic monitoring (96%) and radial artery was the most common site of catheterization (94.6%) followed by posterior tibial (4.3%), and dorsalis pedis arteries (1.1%). The median platelet count closest to the time of insertion, median platelet count while the arterial catheter in situ, coagulation characteristics (INR, PT and APTT) were comparable between the study groups and there was no significant statistical difference.

A total of 7 catheters (15.2%) in the heparin group and 8 catheters (17.4%) in the normal saline were occluded. The difference between these percentages is 2.2%, which was statistically not significant. The median duration of a patent arterial catheter was 47 hours in the heparin group and 35.5 hours in the normal saline group ($P = 0.10$). The reasons for catheter removal in each group has been detailed in **Table I**. Three children died and one child developed swelling due to extravasation of intravenous fluid in the same arm. These events were unrelated to the study intervention. No significant adverse events related to intervention were recorded in either group.

Kaplan–Meier survival analysis curves of patency of arterial catheter showed no differences between study groups ($P = 0.086$) as seen in **Fig. 2**. As the test statistic (2.952) for the log rank test is less than the critical value (3.84) for the Chi-square distribution for the degree of freedom 1 and significance level $\alpha = 0.05$, there was no statistically significant evidence to show that the duration of patency (time to occlusion) is different between the study groups.

The proportion of loss of patency (occlusion) in the heparin group was 0.152 (or 15.2%) and that in the normal saline group was 0.174 (or 17.4%). The difference (D) between the treatment groups was 0.022 (or 2.2%) with a Standard Error of Difference (SED) 0.0769. The upper one-sided 95% confidence interval for D was 0.148 (14.8%). Since the upper bound of the 95% confidence interval (CI) surrounding the difference between the treatment groups was 14.8% which is below the specified noninferiority margin of 15%, normal saline infusion can be considered non-inferior to heparinized saline.

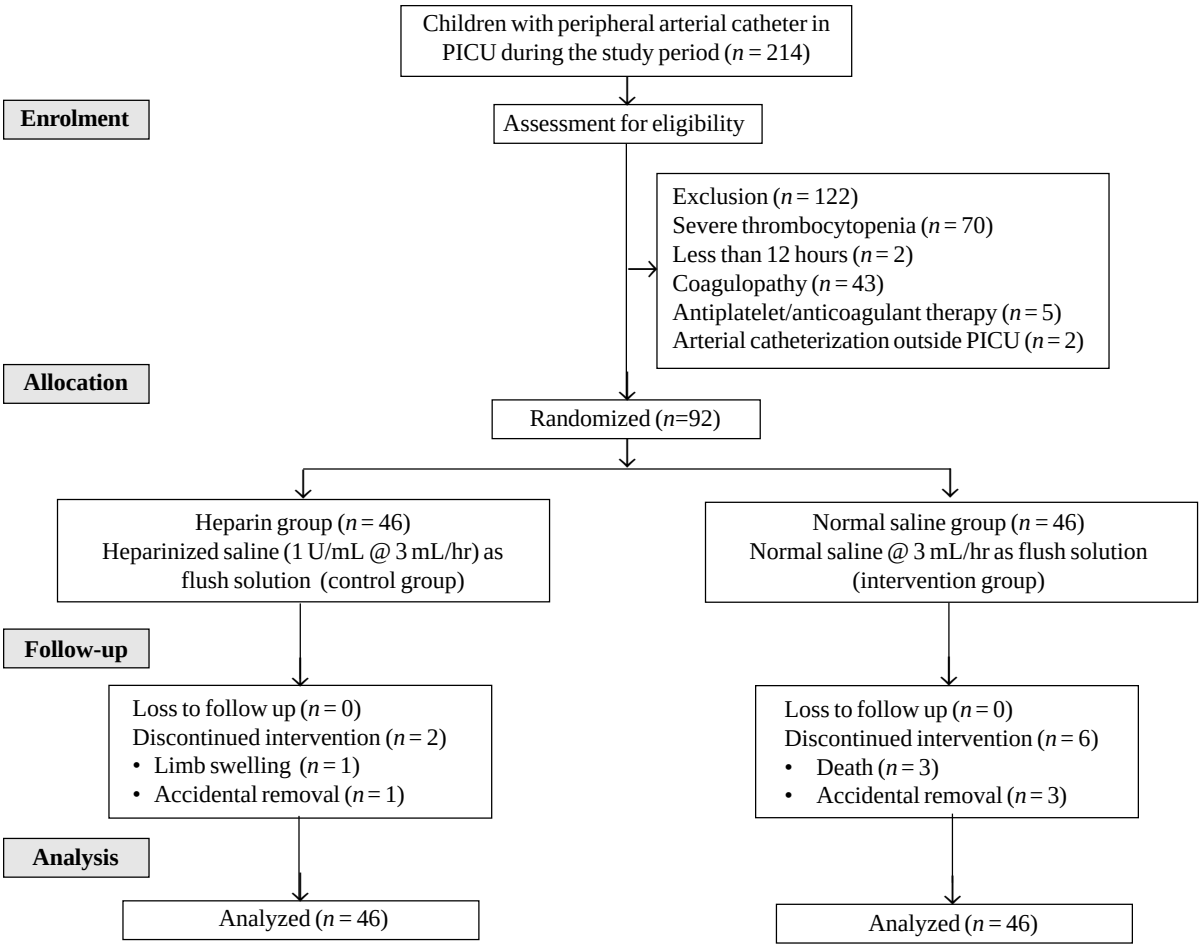


Fig. 1 CONSORT Flow diagram depicting the study participants

DISCUSSION

In this randomised trial, we found no difference between heparin and normal saline infusions in maintaining the patency of arterial catheters in children admitted to PICU. In addition, there was no significant difference in the duration of patent arterial catheter between heparin and normal saline infusions (47 hours vs 35.5 hours, $P = 0.10$). Our study is one of the few studies done exclusively in pediatric population which compared the efficacy of heparinized and normal saline infusions for maintenance of arterial catheter patency. We hypothesised that normal saline could be a safer and cost-effective alternative to heparinized saline, and our results have shown there is no significant difference in the frequency of occlusion between the heparin and normal saline infusion group.

The results of our study are consistent with the findings of Goh et al and Whitta et al where the proportion of non-patency was similar between the heparin and normal saline flush solutions [18,19]. In contrast, our study results differed with the findings of de Neef et al, Kulkarni et al and Clifton et al where the frequency of occlusion was found more in the non heparinized study groups [9, 20,21]. However, except for the study by de Neef et al, all studies were done in adult participants which makes the comparison of results difficult.

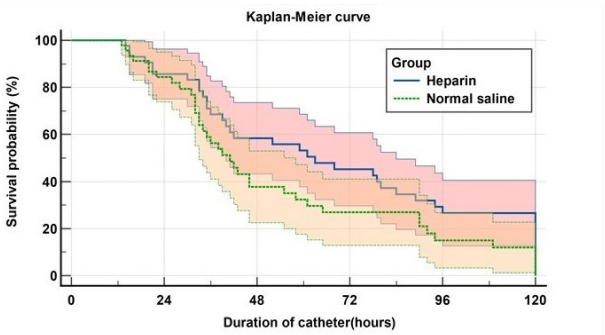
The risk of occlusion of catheter increases with the duration of observation [1, 2, 22]. This finding was seen in our study as well. The use of heparin may, rarely be, associated with bleeding. This may be related to the concentration for heparin used in the flush [8]. However, further research, focusing on different dosages of heparin, is warranted to establish this. We did not encounter any significant adverse clinical effects secondary to the use of heparin, possibly due to low concentrations of heparin (1 U/mL), along with frequent assessment of the limb to identify any risks, therefore minimizing the complications or due to a small sample size.

Table I Baseline Demographic and Clinical Characteristics of Study Participants

	Overall (n=92)	*Heparin group (n=46)*	*Normal saline group (n=46)*
Male gender[a]	48 (52%)	24 (52%)	25 (54%)
Female gender[a]	44 (48%)	22 (48%)	21 (46%)
Age (months)[b]	84 (33.50-132)	73.5 (32.50-144)	90 (35.25-132)
<1 y[a]	12 (13%)	7 (15.2%)	5 (10.9%)
1-3 y[a]	16 (17%)	9 (19.6%)	7 (15.2%)
3-10 y[a]	36 (39%)	14 (30.4%)	22 (47.8%)
>10 y[a]	28 (31%)	16 (34.8%)	12 (26.1%)
Weight (kg)[b]	20 (12-32.75)	19 (12-32.25	20 (10.50-37)
Type of admission[a]			
Medical	86 (93.5%)	43 (93.5%)	43 (93.5%)
Surgical	6 (6.5%)	3 (6.5%)	3 (6.5%)
Reason for catheterization[a]			
Hemodynamic monitoring	88 (96%)	43 (93.5%)	45 (97.8%)
Blood sampling	4 (4%)	3 (6.5%)	1 (2.2%)
Site of cannulation[a]			
Radial	87 (94.6%)	45 (97.8%)	42 (91.3%)
Dorsalis pedis	1 (1.1%)	0 (0%)	1 (2.2%)
Posterior tibial	4 (4.3%)	1 (2.2%)	3 (6.5%)
Number of attempts at cannulation[a]			
1	89 (97%)	46 (100%)	43 (94%)
2	2 (2%)	0	2 (4%)
3	1 (1%)	0	1 (2%)
Platelet count (per mm^3)[b]	288500 (207250-288500)	287500 (246750-341250)	298500 (183000-411000)
INR[b]	1.12 (1.05-1.21)	1.12 (1.04-1.20)	1.11 (1.06-1.25)
Prothrombin time (s)[b]	13 (13-14)	13 (12-14)	13 (13-15)
APTT (s)[b]	31 (28.25-33)	31.50 (29-33)	31 (27.75-32.25)
Duration of a patent arterial catheter (hours)[b]	39.50 (25.25-83)	47 (27.75-94.50)	35.50 (24.50-62)
Reason for catheter removal[a]			
Occlusion	15 (16.3%)	7 (15.2%)	8 (17.4%)
Swelling[c]	1 (1.1%)	1 (2.2%)	0 (0%)
Patient discharged from PICU	49 (53.3%)	26 (56.5%)	23 (50%)
No longer required[d]	20 (21.7%)	11 (23.9%)	9 (19.6%)
Accidental removal	4 (4.3%)	1 (2.2%)	3 (6.5%)
Death[e]	3 (3.3%)	0 (0%)	3 (6.5%)

Values expressed as [a]n (%), [b]median (interquartile range); P >0.05 for all comparisons between both groups. APTT: activated partial thromboplastin time; INR: international normalized ratio. [c]Swelling due to intravenous fluid extravasation, [d]Removed as per physician's orders as no longer needed, [e]Not related to intervention

Heparinized saline is the most common flush used for maintaining the patency of arterial lines in intensive care units [1,2,8]. There have been various studies to identify the best flush solution and to optimize the use of anticoagulants like heparin to balance the benefits and the associated risks [1,2,13,14,16,18,20-22]. However, most of these studies have been primarily conducted in adults with wide variations in methodology. Studies differed in sampling populations, site of arterial cannulation, size of the arterial catheters, concentration and the infusion rates of heparinized flush solutions which made comparisons difficult [1,2]. A comprehensive review of literature and analysis by Kordzadeh et al showed that there was no difference in the patency among the two groups (normal saline and heparin flush) in the first 24 to 48 hours after cannulation; beyond 48 hours after cannulation, heparin was found to be superior to normal saline in maintaining patency [23]. Likewise, the systematic review by Robertson-Malt et al concluded that available evidence is of poor quality because of risk of bias and does not provide sufficient information to support the effects of adding heparin to flush solutions [12]. The current evidence, therefore, is



	Number at risk					
Time (hours)	0	24	48	72	96	120
Heparin	46	35	23	17	10	9
Normal saline	46	35	14	9	5	4

Fig. 2 Kaplan–Meier Survival analysis for patent arterial catheter in heparin and normal saline flush solution groups

inconsistent and does not provide sufficient information to support adding heparin to flush solutions [1].

Our results indicate that the use of normal saline as a flush solution to maintain the patency of arterial catheters in children is safe and effective. Given that many children in PICU require arterial catheters, and in our single centre study we were able to recruit 15 children per month, a larger pediatric trial powered for patient centred outcomes is required and potentially achievable.

Our study does have a few limitations which should be noted. Firstly, this is a single centre study with small number of children, done in an intensive care setting. Geographical, regional and seasonal differences in the incidence of tropical infections might have affected the clinical characteristics of the patients admitted to our unit during the study period. The differences in the catheter insertion techniques by various PICU personnel were not controlled. Also, arterial catheters were removed at different duration due to various reasons and were included in the analysis. However, we included catheters which were *in situ* for at least 12 hours. Finally, observed risk of occlusion of arterial catheter is more than the anticipated risk in both the study groups, a finding that requires further research with a larger sample size. The sample size calculation was done with an anticipated risk of occlusion of 8 % in either group. This was chosen based on the review of literature and results of some previous studies performed in adults comparing the heparin and non-heparinised flush solutions. The reason for the higher incidence of occlusion in our study might have been due to the various reasons ranging from clinical characteristics and the illness of our study population to their genetic predisposition. Noninferiority margin was based on the expected rate of occlusion with heparinised saline and a pre-specified judgment about clinically meaningful difference between the study groups. A narrower noninferiority margin with larger sample size would have given more accurate results. Conclusions on noninferiority of normal saline relative to heparinised saline flush solution were based on intention to treat analysis. Traditionally, intention to treat analysis is considered nonconservative for equivalence and non-inferiority trials, as the inclusion of protocol violators and withdrawals will usually tend to decrease the difference between the two treatment groups and increase the chances of finding equivalence or noninferiority [17]. This therefore, implies further research is warranted to explicate the performance of the normal saline as arterial flush in children. Nevertheless, our outcomes offer some fundamental insights into the use of best flush solution in pediatric population and emphasises the need for further research.

In summary, normal saline infusion was shown to be noninferior to heparinized saline infusion for maintaining patency of arterial catheters in children, and this may benefit clinicians as normal saline would be a safer and cost-effective option. Replication of this study at different sites with larger sample size is needed to confirm the findings.

Ethics approval: IEC of KKCTH, Ref No. ECR/676/Inst/TN/2014/RR-20, dated Feb 01, 2021.
Contributors: KS, SK: Concept and design; SK, GK: Data acquisition; KS, SK: Data analysis and interpretation of data, drafting of the manuscript and statistical analysis; KS, SK, BR, RK: Critical revision of the manuscript for important intellectual content. All authors approved the final version to be published.
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WHAT THIS STUDY ADDS?

- Normal saline infusion is noninferior to heparinized saline infusion in maintaining patency of arterial catheters in children. The use of normal saline as an infusion to maintain the patency of arterial catheters in children is safe and effective.

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ORIGINAL ARTICLE

Mustard Seed Pillow for Prevention of Deformational Plagiocephaly in ≤ 32 Weeks' Gestational Age Infants: An Open Label Randomized Controlled Trial

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ABSTRACT

Objectives: To assess the effectiveness of using mustard seed filled pillows in preventing deformational plagiocephaly (DP) in premature infants.

Method: A prospective open label randomized trial was conducted in a tertiary care hospital in South India. Eligible preterm infants born at ≤32 weeks and <1500 g admitted in the neonatal intensive care unit (NICU) were randomly allocated to the intervention and control groups. In addition to standard nesting, the intervention group was positioned using a mustard pillow, while the control group was positioned using nesting alone. Plagiocephaly was assessed using the Cranial Index (CI), Cranial Vault Asymmetry Index (CVAI) and Argenta classification within the first week and at 4 weeks postnatal age.

Results: Twenty-eight infants, each in the control and intervention groups, were included for analysis. At 4 weeks postnatal age, the intervention group had lower mean (SD) CVAI scores when compared to the control group [3.16 (1.89 vs 7.85 (2.63)] with adjusted odds ratio, aOR (95% CI) of 28.2 (3.8, 210.01), $P < 0.01$. More number of infants in the control group had plagiocephaly measured using Argenta classification [aOR (95% CI) 25.70 (2.80, 235.67), $P < 0.01$]. There were no differences in the Cranial Index scores in the intervention and control groups [aOR (95% CI) 0.41 (0.11, 1.52), $P = 0.184$].

Conclusion: A mustard seed pillow is an easily available and a cost-effective intervention for preventing plagiocephaly in hospitalized preterm infants.

Keywords: *Head shape deformity, Neonatal Intensive Care Unit, Premature infants*

***Trial registration*:** Clinical Trial Registry of India (CTRI)/2019/03/017910) **Published online:** *Jan 09, 2024;* **PII:** *S097475591600579*

INTRODUCTION

Deformational plagiocephaly (DP) is a cranial bone deformity, resulting from the application of unequal external pressure to the cranium after birth [1]. Preterm infants may develop scaphocephaly characterized by bilateral head flattening and/or plagiocephaly characterized by asymmetrical flattening of one side of the skull [2].Thirty eight percent of preterm infants have DP at term equivalent age [3]. A systematic review found positive associations between DP and developmental delay [4].

Early prevention of DP by frequently changing the position of the infant's head, positioning devices, and bedding pillows has been recommended [5]. Commercial devices such as cranial cups or memory foam pillows have been found to be effective in preventing and treating DP. Unfortunately, these are unavailable or expensive to procure in most developing countries [6,7].

Mustard seed pillows are easily available, cost effective, and traditionally used to position infants. Mustard seed pillows can mould to the shape of the infants' head and shoulder, equalizing pressure on the cranium and allowing symmetric positioning without restricting movement [8]. Their use in head and face shaping has been described in Nepal and Rajasthan, India [9,10].

This study aimed at comparing the effectiveness of a combination of mustard seed pillow with standard nesting with isolated standard nesting in the prevention of deformational plagiocephaly in hospitalized preterm infants: by measuring Cranial Index (CI), Cranial Vault Asymmetry Index (CVAI), and Visual Assessment

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(Argenta Classification), assessing motor development using Test of Infant Motor Performance (TIMP), and, comparing body alignment and symmetry with the Infant Positioning Assessment Tool (IPAT).

METHODS

This study was an open-label randomized controlled trial approved by the Institutional Review Board and Ethics Committee and registered with the Clinical Trial Registry India.

It was conducted in a tertiary care neonatal intensive care unit. The period of recruitment was between Jan, 2019 to Sep, 2019. Informed written consent was obtained from parents.

Inclusion criteria were preterm infants of gestational age ≤ 32 weeks and birth weight of less than 1500 g. Neonates with major congenital deformities or infants undergoing interventions that were contradictory to supine positioning were excluded. Once infants were off any invasive respiratory support (mechanical ventilation or continuous positive airway pressure), they were randomly allocated into intervention and control groups. Randomization was done by computer-generated sequences using SAS software and sealed in serially numbered opaque envelopes by the primary investigator (CFS).

A rectangular pillow filled with mustard seeds was used in the intervention group. There were two sizes (based on a pilot study with 15 infants): 11.5 × 9.25 inches filled with 850 grams of mustard seeds, and 9.5 × 8 inches with 450 grams of mustard seeds. The pillows were placed at the mid-scapular level of the infant inferiorly and surrounded by the nesting blankets superiorly and laterally as per standard protocol. The same procedure of standard nesting was used in the control group. The position of the infants was changed every two hours in both groups.

Cranial Index (CI) and Cranial Vault Asymmetry Index (CVAI) were measured in all infants. Both are determined by 3 variables: cranial length, cranial width, and transcranial diagonals measured using a craniometer. CI was calculated by obtaining a ratio of cranial width and cranial length multiplied by 100. Increased values of CI imply worsening of brachycephaly and combined head deformities. It has reported intra-rater reliability Intraclass Correlation Coefficient (ICC) of 0.96 to 0.99 and inter-rater reliability ICC of 0.98 [11,12]. CVAI is obtained by measuring the cranial diagonals of the unaffected side (A) and the affected side (B), where (A > B). CVAI is the difference between the cranial diagonal diameters (A-B) divided by long cranial diagonal diameter (A) multiplied by 100. Severity of DP is classified into 5 levels with higher levels implying worse plagiocephaly. Test-retest reliability (ICC = 0.958) and inter-rater reliability (ICC = 0.874) are reported to be good [11,12].

Argenta Classification is a visual assessment scale used to classify DP into five categories of increasing severity with Type 1 being the least severe and Type 5 being the most severe. Type 1 is restricted to flattening of the back of the skull, Type 2 adds the malposition of the ear, Type 3 adds deformity of the forehead, Type 4 adds a facial deformity and Type 5 adds abnormal vertical growth of the face [13,14]. CI, CVAI and Visual assessment (Argenta Classification) was assessed on two time points, i.e., within week 1 and week 4 (28 -35 days of life).

The infant positioning assessment tool (IPAT) was done once a day. IPAT is a 6-item checklist of infant positioning and symmetry. Scores range from 0 to 12, with optimal scores above 10, and scores < 8 indicating the need to reposition [17]. The Test of Infant Motor Performance (TIMP) is designed to assess functional motor performances of infants from 32 weeks post-conceptional age to 16 weeks after term age. The TIMP has the strongest psychometric properties among neonatal assessments for preterm infants and strong predictive values for later neurodevelopment with the highest predictive accuracy when infants are assessed at 3 months of age [18,19]. The Test of Infant Motor Performance (TIMP) was done at discharge. All outcome assessments were evaluated by a single neonatal therapist (HJ).

The sample size was estimated considering the Cranial Index, as a reference [6]. Using the formula for differences in proportion, the assumed proportion of infants with abnormal CI in the control group being 46% and in the intervention group as 13%; 80% power and alpha error 5%, the calculated study sample was 29 in each group.

Statistical analysis: Descriptive statistics was used. Chisquare and Fisher's exact test were used to determine the association between demographic and other characteristics. Student's t-test was used to compare the difference between the two groups in case of normally distributed data. Logistic regression analysis was done for CI, CVAI, Argenta classification and TIMP for the second assess-ment, adjusting for variables of the study group, gestatio-nal age, birth weight, days on oxygen, perinatal asphyxia, chronic lung disease, and major brain lesion. The line plot was given with descriptive statistics to compare the positioning scores of both groups. Since IPAT scores were performed more than 30 time-points continuously in days the functional t-test methodology under the Functional Data Analysis (FDA) framework was used to assess significant differences in the scores between groups. All tests were two-sided at $\alpha = 0.05$ level of significance. Statistical Package for Social Sciences (SPSS) software Version 21.0 (IBM Corp) was used for analysis.

RESULTS

Fig. 1 depicts the flow of participants in the study and the intervention strategies used. **Table I** presents the baseline characteristics of participants in both groups. There were no significant differences in demographic characteristics, or neonatal complications. However, the control group received significantly longer duration of ventilation and more days of oxygen ($P = 0.02$).

Table II presents the details of various assessments at the two time points of assessment (week 1 and 4). The first assessment showed significantly higher mean scores of CVAI implying higher levels of plagiocephaly in the intervention compared to the controls. At four weeks postnatal age, the intervention group had significantly lower mean CVAI scores when compared to the control group. More infants in the control group had plagiocephaly by Argenta classification. There were no differences in the CI scores or motor performance. Mean positioning scores using IPAT were significantly better in the intervention group compared to the control group. There were no adverse events reported with the use of mustard seed pillows.

When logistic regression analysis adjusting for variables like gestational age, birth weight, days on oxygen, perinatal asphyxia, chronic lung disease, and major brain lesion was done, the intervention group had greater chances of lower CVAI scores compared to the control group at 4 weeks postnatal age, adjusted odds ratio (aOR), 95% confidence interval (CI) of 28.2 (3.8, 210.01), $P < 0.01$. More number of infants in the control group had plagiocephaly measured using Argenta classification [aOR (95% CI) 25.70 (2.80, 235.67), $P < 0.01$]. There were no differences in the Cranial Index scores in the intervention and control groups [aOR (95% CI) 0.41 (0.11, 1.52), $P = 0.184$].

DISCUSSION

Progressive flattening of the skull in premature infants has been attributed to malleability of cranial bones, head turn preference, and inability to spontaneously reposition their head due to a relatively large head mass and poor neck muscle tone [18,19]. Conservative methods such as active repositioning, rotating the head during feedings and sleep, and providing supervised prone time may be used to

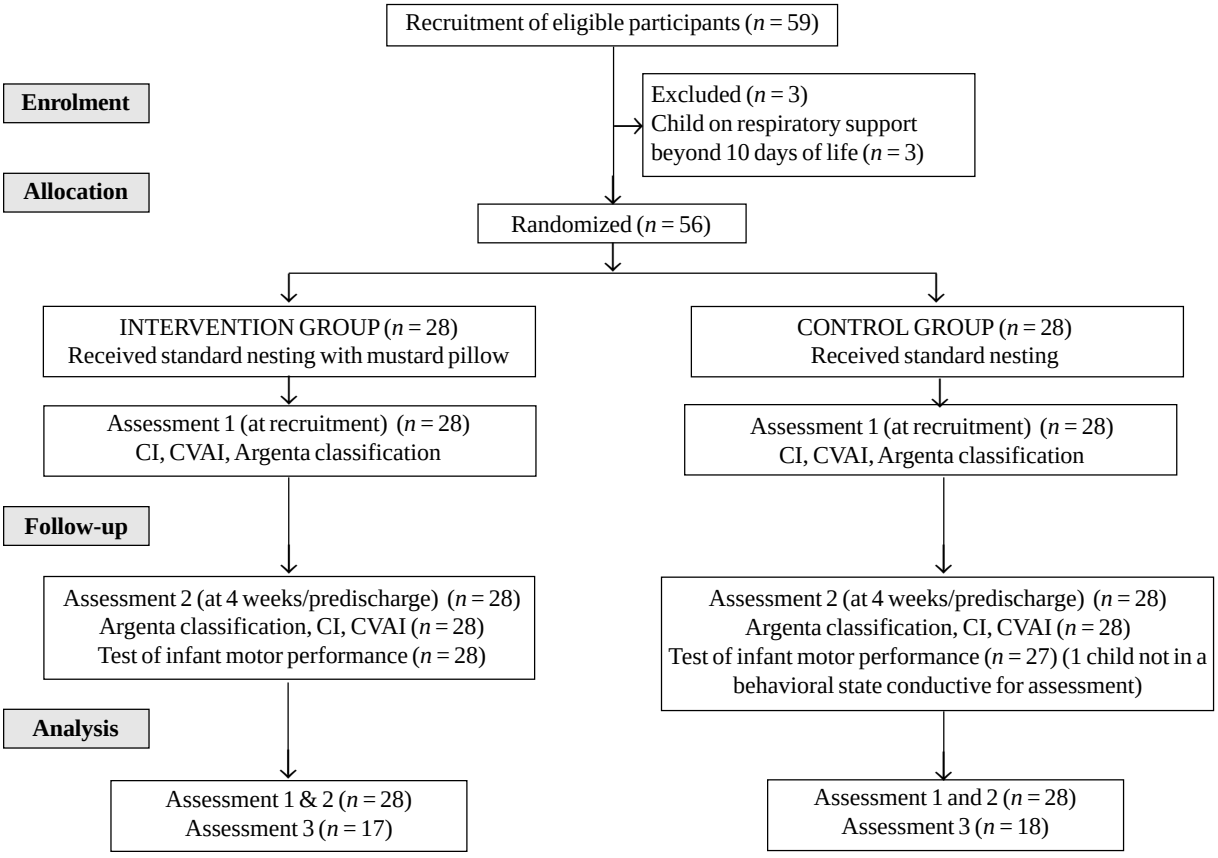

Fig. 1 Flow of participants from enrollment to analysis

Table I Clinical Characteristics of Infants in Control and Intervention Group

Characteristics	*Control group (n = 28)*	*Intervention group (n = 28)*
Gestational age at birth (week)[a]	29.50 (1.6)	29.71 (1.5)
Birth weight (g)[a]	1175.7 (232.3)	1146.2 (223.3)
Length at birth (cm)[a]	35.75 (3.0)	36.61 (2.7)
Head circumference (cm)[a]	26.50 (1.4)	26.73 (1.6)
Length of hospital stay (days)[a]	48.50 (21.0)	46.93 (19.1)
Male gender	17 (60)	18 (64)
Twin gestation	7 (25)	7 (25)
Type of delivery		
Normal vaginal delivery	1 (4)	5 (18)
Lower segment cesarean section	25 (89)	23 (82)
Breech extraction/ Instrumental	2 (8)	0
Perinatal asphyxia	6 (21.4)	4 (14.3)
Ventilated	25 (89.3)	23 (82.1)
Hours of ventilation[a]	15.02 (18.7)	3.15 (6.3)
Continuous positive airway pressure (CPAP)	25 (44.6)	21 (37.5)
Hours on CPAP[a]	42.10 (43.0)	29.71 (29.8)
Apneic episodes	15 (53.6)	11 (39.3)
Days on oxygen[a]	18.17 (34.9)	3.75 (9.6)
Hyaline membrane disease	9 (32.1)	7 (25.0)
Bronchopulmonary dysplasia	2 (7.1)	2 (7.1)
Hypoglycemia	5 (17.9)	3 (10.7)
Septicemia	6 (21.4)	2 (7.1)
Major brain lesion on cranial ultrasound	0	4 (14.3)

Values expressed as n (%) or mean (SD)[a]. P > 0.05 for all variables except hours of ventilation and days on oxygen where P = 0.02 and P = 0.04, respectively.

prevent DP, but are not always successful or feasible in hospitals with high staff patient ratios [6,20]. Pillows were found superior and easier to use than stretching exercises in correcting positional head deformities in infants in one study [5]. Pressure relief positioners (air mattresses, waterbeds, water pillows, therapeutic mattresses, and gel pillows) have been used previously with some success in preventing DP [21]. However, these devices are expensive and may not correct all types of plagiocephaly [22]. Donut-shaped gel pillows effectively disperse pressure away from the occiput, but transfer it to a narrow region of scalp tissue, increasing the risk of pressure injuries [23].

Our study showed that fewer hospitalized preterm infants, when positioned on a mustard seed pillow with additional nesting, showed DP at 4 weeks postnatal age compared to infants using isolated nesting by CVAI index and Argenta classification.

There was no significant difference in the Cranial index scores of interventional and control groups at the second assessment. This may imply that mustard seed pillows cannot prevent brachycephaly. Infants in our study were predominantly placed in the supine position, which predisposes to brachycephaly per se. Other studies report similar findings while evaluating positioning pillows for correcting DP; there was no decrease in brachycephaly, but significantly lower CVAI scores in the pillow groups [5,7].

Our study found no differences in the motor performance of infants between groups measured at 4 weeks. Several studies have found associations with a mutually predictive ability between DP and asymmetric motor performance of premature infants at term equivalent age, 3 months and 6 months [7,24]. A possible reason why this association was not found in the present study may be since TIMP was administered at around 36 weeks corrected age. This may be too early to detect a difference in motor development. Also, this study was not adequately powered to assess motor outcomes. We recommend that future studies evaluate neuro developmental outcomes after a more prolonged duration.

The results of the IPAT indicate that the intervention group was consistently more optimally positioned than the control group. The mustard pillow supports the head, neck, and shoulders, thus facilitating flexion and midline positioning and contributing to optimal positioning. Standard recommendations for positioning infants in the NICU include placing the head near the midline, with support under the shoulder and humerus to facilitate shoulder protraction, allowing hands to touch the chest or mouth [18]. During the study, nurses reported the need to frequently reposition the infants who were placed on the pillow when head end elevation was indicated.

This study was the first to look at the effectiveness of mustard pillows in preventing DP in preterm infants in the NICU. There are however, a few limitations. The outcome assessor was not blinded to group allocation since it was not feasible in our setting. Since there was a single assessor, inter-observer variability could not be measured. Baseline neurological status and associations of neonatal complications such as osteopenia and other cranial pathologies were not evaluated. The study was conducted in a tertiary care intensive care unit, and therefore generalizability of the results to primary and secondary care settings is not known. We conclude that Mustard seed pillow is an easily available and cost-effective intervention for preventing plagiocephaly in hospitalized preterm infants.

Table II Comparison of CVAI, CI, Argenta Classification and TIMP in the Intervention and Control Groups

	Intervention group (n = 28)	*Control group (n = 28)*	*P value*	*Intervention group (n = 28)*	*Control group (n = 28)*	*P value*
	At recruitment			*4 weeks postnatal age*		
Head circumference (cm)[a]	26.72 (1.56)	26.50 (1.39)	0.56	29.22 (1.85)	29.61 (1.12)	0.34
Cranial vault asymmetry index (CVAI)[a]	4.45 (2.02)	2.54 (1.24)	< 0.01	3.16 (1.89)	7.85 (2.63)	< 0.01
CVAI *classification*[b]						
Level 1	11 (39)	22 (79)		18 (64)	2 (7)	
Level 2	15 (54)	6 (21)		9 (32)	6 (21)	
Level 3	0	0	< 0.01	0	8 (29)	< 0.01
Level 4	2 (7)	0		1 (4)	9 (32)	
Level 5	0	0		0	3 (11)	
Cranial Index (CI)[b]						
Normocephaly	11(39)	7 (25)		12 (42)	14 (50)	
Dolicocephaly	3 (10)	7 (25)	0.33	8 (28)	10 (35)	0.45
Brachycephaly	14 (50)	14 (50)		8 (28)	4 (14)	
Argenta classification[b]						
No plagiocephaly	19 (68)	24 (86)		20 (71)	2 (7)	
Type 1	9 (32)	4 (14)		6 (21)	11 (39)	
Type 2	-	-		1 (4)	10 (36)	< 0.01
Type 3	-	-	0.20	1 (4)	3 (11)	
Type 4	-	-		0	0	
Type 5	-	-		0	2 (7)	
TIMP (n = 27/28)						
Raw score[a]				33 (8.7)	34.7 (8.6)	0.45
Classification[b]						
Average				4 (14)	3 (11)	
Low average				3 (10)	5 (18)	0.86
Below average				17 (60)	15 (56)	
Far below average				4 (14)	4 (15)	
Infant positioning assessment tool						
Number of days scored[a]; (range)				20.9 (8.0) (9-42)	19.64 (8.3) (8-36)	0.55
Score[a]				9.12 (1.39)	7.41 (1.69)	< 0.01

Values in mean (SD)[a], n (%)[b], TIMP: Test of infant motor performance

Ethical Clearance: Institutional Review Board and Ethics Committee of Christian Medical College, Vellore (IRB number 11649)

Trial Registry: Clinical Trial Registry of India (CTRI/2019/03/017910).

Contributors: CFS: Conceptualized and designed the study, data collection, analysis and interpretation, drafted and revised the manuscript. HJ: Study design, supervised data acquisition and analysis, interpretation of data, revised the manuscript. RJS: Study design, supervised data collection, interpretation of data, and revised the manuscript. RK: Data analysis and interpretation, revised the manuscript. MK: Study design, data acquisition and interpretation, revised the manuscript.

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WHAT THIS STUDY ADDS?

- Mustard seed pillows can be used in hospitalized preterm infants.
- The use of mustard seed pillow in addition to standard nesting is effective in preventing deformational plagiocephaly during hospital stay.

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ORIGINAL ARTICLE

Segmental Limb Length Measurements in Term Neonates From Southern India

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ABSTRACT

Objective: To develop gender and gestational age-specific reference standards for segmental limb lengths in term neonates.

Methods: A cross-sectional study was conducted in a tertiary hospital in Tamil Nadu from June, 2019 to October, 2020. Term neonates were included through convenient sampling. Segmental length of upper and lower limbs was measured using non-stretchable steel measuring tape and total body length was measured with infantometer. Gestational age-specific mean length of all limb segments and segmental index with reference to total body length were calculated.

Result: 950 term neonates were recruited. Their mean (SD) birth weight (kg) was 2.98 (0.34) and 17.5% were small for gestational age. Their mean (SD) total upper limb length (cm) and total lower limb length (cm) were 20.96 (1.22) and 19.6 (1.18), respectively. Gender-based difference was noted in total body and upper limb segment lengths. Segmental limb lengths had negligible positive correlation with gestational age but had a moderate positive correlation with total body length.

Conclusion: Gender and gestational age-specific segmental limb lengths standards may help to identify abnormal limb lengths in neonates at birth.

Key words: *Anthropometry, Total body length*

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INTRODUCTION

Shortening of long bones are observed in skeletal dysplasias, genetic syndromes, intrauterine growth restriction, chromosomal anomalies and constitutionally small fetuses [1,2]. Unlike intrauterine limb length reference standards, there is a paucity of data on neonatal limb length standards; few studies from India and Israel were published three decades ago [3-5]. Recent birth cohorts have greater size at birth compared to those born in 1990s [6]. Hence, this study was undertaken to establish normal segmental limb length standards for healthy neonates.

METHODS

This prospective cross-sectional study was done in a tertiary hospital in Tamil Nadu, India, from June, 2019 to October, 2020. The primary objective was to create a reference standard for upper and lower limb segmental lengths for term neonates. Secondary objective was to determine gender difference in limb lengths, to correlate segmental limb length with gestational age and total body length, and to calculate segmental limb length index (SLLI).

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Neonates with gestational age between 37 and $41^{6/7}$ weeks were included. The completed gestational age in weeks was preferably assigned using the first trimester ultrasound report; if not it was calculated from last menstrual period. Sick neonates who were in neonatal intensive care unit during the scheduled time of length measurement were excluded.

Convenient sampling was planned and approval from the Institutional Human Ethics Committee was obtained. Informed written consent was taken from either of the parents and measurement was done in a warm, calm room with warm, dry washed hands and clean equipment. The measurements were taken in right extremity, between 24-72 hours of age and when the neonate was calm. The measurements were taken by the principal investigator with the help of a trained nurse. First the bony points were marked with erasable surgical skin marker pen (Office-mate-Sterile, Gamma Radiated, Non-toxic ink). A standardized non-stretchable steel measuring tape (Freeman top line – EEC approved, FMI Limited) graduated in millimetres was used. The total body length was measured

using infantometer scale (Seca). Birth weight was measured using a digital weighing scale (Phoenix NBY 20, Nitiraj engineering Limited) and small for gestational age (SGA) was identified with Intergrowth 21 charts [7].

All measurements were taken twice for each parameter, to the nearest of 0.1 cm; an average of these two measurements was calculated for use. The instruments were cleaned with 70% isopropyl alcohol after each use and the skin markings on neonate's body were erased with disinfectant handrub solution containing 70% ethanol and 0.5% chlorhexidine.

Total upper limb length was measured from the tip of acromion process to the tip of middle finger, with the upper limb parallel to body and elbow in maximum extension. Arm length was measured from the tip of acromion process to the tip of olecranon process, with elbow bent at 90°. The forearm was measured from the tip of olecranon process to the distal end of styloid process of radius, with the elbow bent at 90°. Hand length was measured from the distal wrist crease to the tip of middle finger, and the middle finger length was obtained by measuring the distance from the proximal flexion crease of middle finger to its tip.

Total lower limb length was measured from the upper tip of greater trochanter to the lower tip of lateral malleolus, with the knee maintained in maximum extension. Thigh length was measured from the upper tip of greater trochanter to the lower tip of lateral femoral condyle with knee flexed at 90°. The leg length was measured from the lower tip of lateral femoral condyle to the lower tip of lateral malleolus, with the knee flexed at 90°. The foot length was measured from the posterior prominence of heel to the tip of big toe, with the foot and big toe maintained in neutral position.

Total body length (cm) was measured by placing the neonate on an infantometer scale fixed to a wooden table. Measurement was taken with the neonate's head touching the fixed plastic frame, body held straight by the assistant, knee extended as much as possible by the investigator and sole of feet touching the mobile plastic frame.

Table I Mean Segmental Limb Length and Median Total Body Length of Term Neonates (*n* = 950)

Gestational age	*37 weeks*		*38 weeks*		*39 weeks*		*40 weeks*	
	Boys (n =101)	*Girls (n = 83)*	*Boys (n = 184)*	*Girls (n = 202)*	*Boys (n = 100)*	*Girls (n = 134)*	*Boys (n = 75)*	*Girls (n = 71)*
Birth weight (kg)[a]	2.84 (0.40)	2.79 (0.41)	3.04 (0.36)	2.86 (0.35)	3.06 (0.32)	3.06 (0.31)	3.15 (0.31)	3.12 (0.29)
Small for gestational age (%)	12.8	13.2	9	10.8	20	9.7	18.6	25
Total upper limb length (cm)[a,c]	20.73 (1.09)	20.22 (1.07)	21.19 (1.04)	20.55 (1.02)	21.22 (1.3)	21.11 (1.19)	21.7 (0.98)	21.41 (0.96)
Arm length (cm)[a,c]	9.3 (0.40)	9.19 (0.38)	9.45 (0.43)	9.28 (0.41)	9.56 (0.38)	9.47 (0.37)	9.63 (0.41)	9.56 (0.39)
Forearm length (cm)[a]	7.82 (0.46)	7.68 (0.44)	8.02 (0.48)	7.88 (0.46)	8.04 (0.43)	7.95 (0.41)	8.19 (0.47)	8.09 (0.45)
Hand length (cm)[a,c]	6.50 (0.31)	6.43 (0.29)	6.55 (0.30)	6.47 (0.28)	6.63 (0.26)	6.59 (0.24)	6.72 (0.25)	6.66 (0.23)
Middle finger length (cm)[a]	2.76 (0.19)	2.73 (0.17)	2.83 (0.18)	2.75 (0.16)	2.83 (0.17)	2.79 (0.15)	2.87 (0.17)	2.84 (0.15)
Total lower limb length (cm)[a]	19.26 (0.98)	19.01 (0.96)	19.61 (1.4)	19.20 (1.29)	19.85 (1.4)	19.75 (1.29)	19.93 (1.04)	20.83 (1.02)
Thigh length (cm)[a]	8.66 (0.50)	8.5 (0.48)	8.68 (0.51)	8.56 (0.49)	8.77 (0.45)	8.74 (0.43)	8.88 (0.52)	8.92 (0.50)
Leg length (cm)[a]	9.39 (0.48)	9.20 (0.46)	9.50 (0.43)	9.34 (0.41)	9.55 (0.40)	9.53 (0.38)	9.72 (0.46)	10.14 (0.44)
Foot length (cm)[a]	7.72 (0.38)	7.81 (0.36)	7.88 (0.35)	7.88 (0.33)	8.05 (0.31)	7.91 (0.29)	8.28 (0.32)	8.01 (0.30)
Total body length (cm)[b,c]	47.75 (46, 49) (*n* = 46)	48 (46, 49) (*n* = 39)	49.25 (48, 51) (*n* = 74)	48 (47, 49) (*n* = 89)	50 (49, 51) (*n* = 49)	49 (48, 50) (*n* = 62)	49 (48, 50) (*n* = 26)	49 (48, 50) (*n* = 23)

Value in [a]mean (SD) or [b]median (IQR); [c]P<0.05

Statistical analysis: Mean (SD) or median (IQR) was calculated for continuous data. Correlation coefficient was used to measure the strength of relationship between gestational age and limb lengths. SLLI was calculated as (segmental limb length ÷ total body length) X 100. SPSS statistics for Windows, Version 24 (IBM Corp.) was used for data analyses. $P < 0.05$ was considered significant.

RESULTS

Total live births in hospital during the study period was 7599; term neonates were 6380 and 5847 were eligible for the study. Convenient sampling yielded 950 term neonates with 460 (48.4%) boys and 490 (51.6%) girls. Their mean (SD) birth weight was 2.98 (0.34) kg and 17.5% were SGA. Mean (SD) total upper limb length and total lower limb length were 20.96 (1.22) cm and 19.6 (1.18) cm respectively. Gender wise mean limb lengths for each gestational age was calculated (**Table I**). Total body length, total upper limb length, arm length and hand length showed significant difference between genders. Overall, the mean length of each limb segment increased as the gestational age increases but it had a negligible positive correlation.

Due to logistic reasons related to rapid transformation of many wards into COVID wards during the study, infantometer was available to measure total body length only for 408 neonates; 195 boys and 213 girls. A moderate positive correlation was observed between segmental limb lengths and total body length; correlation was high for thigh length and total lower limb length (**Table II**). SLLI was calculated only for neonates whose total body length was available. SLLI of each limb segment remained constant with no significant difference across the gestational age irrespective of the gender (**Table III**).

Table II Correlation Between Segmental Limb Length, Gestational Age and Total Body Length Among Term Neonates

Segmental limb length	*Correlation coefficient (r)*	
	Gestational age (n = 950)	*Total body length (n = 408)*
Total upper limb length	0.312	0.620
Forearm length	0.294	0.630
Arm length	0.241	0.680
Hand length	0.251	0.547
Middle finger length	0.205	0.545
Total lower limb length	0.247	0.713
Thigh length	0.247	0.713
Leg length	0.245	0.620
Foot length	0.270	0.544

Table III Segmental Limb Length Index of the Term Neonates (*n* = 408)

Gestational age	*37 weeks (n = 85)*		*38 weeks (n = 163)*		*39 weeks (n = 111)*		*40 weeks (n =4 9)*	
	Boys (n = 46)	*Girls (n = 39)*	*Boys (n = 74)*	*Girls (n = 89)*	*Boys (n = 49)*	*Girls (n = 62)*	*Boys (n = 26)*	*Girls (n = 23)*
Birth weight (kg)	2.71 (2.51, 2.94)	2.7 (2.5, 3.12)	3.09 (2.88, 3.29)	2.8 (2.64, 3.06)	3.1 (2.96, 3.33)	3.06 (2.79, 3.23)	3.09 (2.91, 3.31)	3.09 (2.86, 3.26)
SGA (%)[a]	17.3	10.2	10.8	14.6	12.2	12.9	13	12.5
Total upper limb length (cm)	43 (42.39, 43.97)	42.55 (41.67, 43.7)	42.86 (42.02, 43.75)	42.71 (41.89, 43.75)	42.86 (42, 44.06)	42.81 (42, 43.81)	43.14 (41.84, 44.12)	43.75 (42.11, 44.26)
Arm length (cm)	19.56 (18.97, 19.79)	19.39 (19, 19.57)	19.18 (18.82, 19.59)	19.39 (19, 19.79)	19 (18.79, 19.61)	19.08 (18.91, 19.59)	19.38 (18.94, 19.61)	19.39 (18.78, 20)
Forearm length (cm)	15.94 (15.55, 16.34)	15.68 (15.31, 16.13)	15.92 (15.51, 16.33)	15.96 (15.47, 16.3)	15.88 (15.47, 16)	15.63 (15.31, 16.01)	15.69 (15.38, 16.01)	15.96 (15.46, 16.33)
Hand length (cm)	13.54 (13.33, 13.97)	13.67 (13.4, 13.96)	13.54 (13.23, 13.83)	13.62 (13.33, 13.83)	13.46 (13.2, 13.76)	13.47 (13.27, 13.81)	13.5 (13.25, 13.73)	13.67 (13.54, 14.08)
Middle finger length (cm)	5.71 (5.51, 5.87)	5.71 (5.51, 5.87)	5.63 (5.45, 5.86)	5.63 (5.51, 5.74)	5.71 (5.47, 5.98)	5.6 (5.51, 5.74)	5.64 (5.49, 5.9)	5.83 (5.6, 5.92)
Total lower limb length (cm)	41.3 (40, 42.39)	40.82 (40.22, 41.74)	41.09 (40.22, 41.67)	41.05 (40, 42)	41.02 (40.2, 42)	41.5 (40.77, 42.37)	41.18 (40.29, 42)	41.24 (40.82, 42.86)
Thigh length (cm)	17.71 (17.35, 18.02)	17.71 (17.35, 18.09)	17.53 (17.16, 17.72)	17.55 (17.19, 17.94)	17.65 (17.16, 18)	17.71 (17.34, 18)	17.65 (17.31, 17.78)	17.71 (17.35, 18.37)
Leg length (cm)	19.57 (19.16, 20)	19.57 (19.15, 20)	19.49 (19.01, 19.79)	19.57 (19.08, 19.8)	19.57 (19, 20)	19.39 (19, 19.8)	19.61 (19, 19.65)	19.6 (19.2, 20)
Foot length (cm)	16.1 (15.63, 16.43)	15.96 (15.63, 16.33)	15.96 (15.55, 16.33)	15.96 (15.63, 16.3)	15.96 (15.66, 16.26)	16 (15.6, 16.34)	15.88 (15.63, 16.33)	16 (15.88, 16.33)

Values expressed as median (interquartile range) or [a]percentage; SGA: small for gestational age

WHAT THIS STUDY ADDS?

- Gender-specific, gestational age-wise segmental limb length standards for term neonates and corresponding segmental limb length index were developed.

DISCUSSION

Clinical assessment of limb lengths in neonates may be misleading and thus limb length standards are needed to identify limb length abnormalities in neonates [3,4]. Such standards will also help to confirm short long bones identified in the fetal period. Short long bones in fetuses were defined sonologically as bone length > 2 SD below the mean for gestational age [1,2]. Same criteria can be adopted for interpreting limb length measurements in neonates. The present study has found gender related differences in some segmental limb lengths. But studies from Israel, had found no significant difference in limb lengths between boys and girls. These studies had only 68 neonates in 37- 40 weeks gestation out of total 198 [3,4]. Intergrowth 21, a recent reference chart to assess size of neonate at birth which includes body length, also gives separate standards for boys and girls [7].

Though the segmental limb lengths increased with increasing gestational age as observed in other studies [3-5], it had negligible positive correlation with gestational age unlike a previous study [5]. However, total body length had moderate positive correlation with various limb segment measurements. Thus, the SLLI of various limb segments remained same across all gestational age in both genders. Previously authors [3,4] have calculated segmental index with total limb length in denominator and had found it to remain same across all gestational ages. In the present study, since total limb length positively correlated with total body length, total body length was used a common denominator for both upper and lower limb indices. Such gestational age independent indices may provide more meaningful interpretation of limb lengths than absolute segmental limb lengths, especially when correct gestational age was not known.

Length of all segments of upper and lower limbs were measured using standard technique similar to other studies [3-5]. In addition, derivation of SLLI using total body length adds strength and novelty to this study. Gender based representation of normal values is unique to this study. The postnatal age and landmarks for limb segment measurements were similar to previous studies, though Sivan et al and Merlob et al had used sliding caliper for measurement. We have not collected data about socio-economic status of the study participants which can affect their size at birth [8]. The study was done in general ward of a medical college hospital which mainly caters to people with low and low middle class socioeconomic status. As intrauterine growth restriction can affect the neonate's body stature at birth, its assessment would have helped to select only adequately nourished neonates to develop the limb standards [9]. No data were obtained for 41 weeks category, as no neonate was born beyond 40 weeks of gestation. Further multicentric research with larger sample size and addressing the above limitations is needed.

The segmental limb length standards, which are gender and gestational age specific, may help in identifying neonates with abnormal limb lengths at birth. Comparing the segmental limb length with total body length may be more informative than absolute limb lengths.

Ethics clearance: Institutional Human Ethics Committee of PSG Institute of Medical Sciences & Research; No.19/126, dated Jun 10, 2019.
Contributors: IC: Conception, study design, data collection, drafted the paper and revised it; RS: Conception, study design, revision of manuscript for important intellectual content, analysis and interpretation of data. SK: Study design, statistical analysis. The final manuscript was approved by all.
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ORIGINAL ARTICLE

Spectrum of Primary Immunodeficiency Disorders in Hospitalized Children: Multicentric Data From Kolkata

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ABSTRACT

Objective: To evaluate the incidence and types of primary immunodeficiency diseases (PIDs) in hospitalized children with infection.

Methods: This prospective study was conducted in five tertiary-care facilities in Kolkata over two consecutive years between November 1, 2018 and October 31, 2020. We included all children aged upto 12years who were hospitalized and screened them for PID. Children were screened for suspected IPD using Jeffrey Modell Foundation (JMF) Criteria; any child who satisfied at least 2 out of 10 warning signs was further evaluated for PIDs.

Results: Out of 33,204 hospital admissions, 50 children satisfied JMF criteria. Out of 50 children screened during the study period, 27 were finally diagnosed with an underlying PID, with a prevalence of 1 in 1000 hospitalized children. Majority (37.03%) of them had antibody deficiency followed by phagocytic defect (33.3%). Chronic granulomatous disease was the commonest PID followed by common variable immunodeficiency. Around 62.97% children presented with respiratory infections and overall *Acinetobacter baumannii* was the commonest isolated organism.

Conclusion: Our study presents the first cohort of PID from eastern India. A methodical step-wise clinical and diagnostic approach can facilitate early diagnosis and timely therapeutic interventions.

Keywords: *Acinetobacter baumannii, Chronic granulomatous disease, Evaluation, Management*

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INTRODUCTION

Incidence of primary immunodeficiency diseases (PID), once considered as a rare disease, is increasing with the availability of advanced diagnostic modalities [1]. The reported prevalence of PID is as high as 1:1200 in the general population worldwide [1,2]. However, to the best of our knowledge, the exact nationwide incidence of PID in India is not well described. Herein, we have attempted to estimate the load of PID in hospitalized pediatric population, distribution pattern of various categories of PIDs along with the frequency of warning signs and critical parameters for evaluation from eastern India.

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METHODS

A prospective observational study was conducted over a period of two years in the pediatric wards of five different hospitals in Kolkata to estimate the prevalence of PIDs in hospitalized children. All hospitalized children of below twelve years were screened for PIDs between November 1, 2018 and October 31, 2020. A patient was clinically suspected to have PID if he/she fulfilled two or more criteria of Jeffrey Modell Foundation (JMF) warning signs [3]. Patients with two or more warning criteria were more likely to have underlying PIDs, hence were included in our cohort by purposive sampling technique.

All the children, included as study participants, were examined thoroughly. Demographic details, detailed past medical history such as parental consanguinity, family history of PID, history of maternal abortion or sibling loss, adverse events following immunization (AEFI), and the frequency of hospital stay were recorded in a predesigned

proforma. Routine complete blood count, absolute neutrophil count, absolute lymphocyte count, erythrocytes sedimentation rate (ESR), micro platelets in peripheral blood smear, platelet volume, platelet count, blood sugar, liver function test and C-reactive protein (CRP) levels was assayed for all the children. Every suspected patient was subjected to specific laboratory tests to determine the underlying PID. Serum immunoglobulin (IgG, IgM, IgE and IgA subclasses) concentration was measured using a SIEMENS-BN ProSpec® system Nephelometer at the designated immunology laboratory. Analysis of lymphocyte subsets was done by Flow cytometry (BD FACS Verse™) machine to estimate B- and T-cell subtypes count. Dihydrorhodamine (DHR) test and flow cytometry were performed to detect the phagocytic defect-specific cell markers. The diseases were classified based on results of immunoglobulin profile and flow cytometry (B- and T-cell lineage markers) including DHR assay. Leucocyte adhesion deficiency type 1 (LAD-1) was diagnosed by the absence of CD-18 expression in flow cytometry. Serum complement (C3, C4) levels, anti-nuclear antibody (ANA) titer and rheumatoid factor (RF) assessment were done using nephelometry.

These tests were repeated after three months except in situations where the test reports were grossly abnormal. When the reports were identical on both occasions, the diagnosis was made accordingly. The samples were taken prior to initiation of any therapy. Wherever required, blood samples were sent to specialized laboratories for confirmation of diagnosis. The children with "diagnosed PID" were further classified in five subgroups based on predominant immune component involvement. Patients who already received treatment for PID, those with HIV infection or receiving chemotherapy were excluded.

Ethical clearance was taken from the institutional ethical committee of respective hospitals prior to the study. A preformed consent was taken in written form from the parents or local guardians of the children before inclusion. The study was conducted as per declarations of Helsinki.

Statistical analysis: Statistical analysis was performed using SPSS 20 software. The categorical data were represented as frequency (*n*) and percentage (%); the continuous variables were expressed as mean (± standard deviation, SD) and median (interquartile range, IQR) for parametric and non-parametric variables respectively. Categorical variables were compared between groups using Chi-square and Fisher exact test. Comparison of distribution of continuous non-parametric variables was done using Mann-Whitney *U* test for two samples. The *P* value < 0.05 was considered significant.

RESULTS

Out of 33,204 hospital admissions, 50 children satisfied the JMF criteria. A history of 4 or more ear infections in one year was the commonest presentation (55.5%), followed by recurrent deep skin infections or organ abscess (40.7%), recurrent pneumonia (37%), and a need for intravenous antibiotics to clear infection (22.2%). Serious recurrent sinus infection in 1 year was reported in only 3.7% children. Overall, 27 (54%) children had PIDs with a prevalence of 93.24 per 100,000 hospitalized children (~1/1000 admission).

The clinicodemographic variables like gender, parental consanguinity, socioeconomic status etc. in children with PID (*n* = 27) were compared with those without PID (*n* = 23) (**Table I**). Out of 27 cases of PIDs, 19 (70%) were infants with female preponderance. The clinicodemographic profiles in different PID subgroups were analyzed (**Table II**). The two most common abnormalities were antibody deficiency (37%) and phagocytic function defect (33.3%). Others were combined deficiency (7.4%),

Table I Clinico-demographic Profile of Children with Suspected and Confirmed Primary Immunodeficiency Disease (PID)

	Suspected PID (n = 50)	*Confirmed PID (n = 27)*	*Non-PID (n = 23)*
Age (months)	9.0 (4.0-72.0)	8.0 (4.0-24.0)	32.0 (7.5-78.0)
Age groups[a]			
≤ 1 month	5 (10.0)	2 (7.4)	3 (13.0)
> 1-12 months	22 (44.0)	16 (59.2)	6 (26.1)
> 1-5 years	10 (20.0)	4 (14.8)	6 (26.1)
> 5 years	13 (26.0)	5 (18.5)	8 (34.8)
Gender[a]			
Male	27 (54.0)	12 (44.4)	15 (65.2)
Female	23 (46.0)	15 (55.5)	8 (34.8)
Parental consanguinity[a]	10 (20.0)	8 (29.6)	2 (8.7)
Family history[a]	12 (24.0)	7 (25.9)	5 (21.74)
High income group[a]	4 (8.0)	2 (7.4)	2 (8.7)
Medium income group[a]	18 (36.0)	9 (33.3)	9 (39.1)
Low income group[a]	28 (56.0)	16 (59.3)	12 (52.2)
AEFI[a]	2 (4.0)	1 (3.7)	1 (4.35)
Number of hospital admissions	2.0 (1.0-4.0)	3.0 (1.0-4.0)	2.0 (1.0-3.0)
First time admission	18 (36.0)	8 (29.6)	10 (43.5)
< 4 times[a]	19 (38.0)	11 (40.7)	8 (34.8)
≥ 4 times[a]	13 (26.0)	8 (29.6)	5 (21.7)

The values are expressed as median (IQR) and [a]n (%). P > 0.05 for comparison between all variables of comparable groups. AEFI: Adverse event following vaccination

Table II Clinicodemographic Profile of Children with Different Primary Immunodeficiency Diseases (PIDs)

	Total PID (n = 27)	*Innate defect (n = 3)*	*Phagocytic defect (n = 9)*	*Combined deficiency (n = 2)*	*Syndromic mmunodeficiency (n = 3)*	*Antibody deficiency (n = 10)*
Age (months)[a]	8.0 (4.0-27.0)	72.0 (40.0-150.0)	4.0 (3.0-11.0)	5.0 (4.0-6.0)	96.0 (57.0-102.0)	7.0 (4.0-9.0)
Gender, Males	12 (44.4)	1 (33.3)	5 (55.5)	0	2 (66.7)	4 (40.0)
Consanguinity	8 (29.6)	1 (33.3)	3 (33.3)	1 (50.0)	0	3 (30.0)
Family history	7 (25.9)	0	2 (22.2)	2 (100.0)	0	3 (30.0)
Hospital admission frequency[a]	3.0 (1.0-4.0)	2.0 (1.5-2.0)	1.5 (1.0-3.0)	2.0 (1.0-3.0)	5.0 (4.5-5.5)	4.0 (3.0-4.0)
AEFI	1 (3.7)	1 (33.3)	0	0	0	0
Negative blood culture	12 (44.4)	1 (33.3)	3 (33.3)	2 (100.0)	2 (66.7)	4 (40.0)
Positive blood culture	16 (59.3)	2 (66.7)	8 (88.8)	1 (50.0)	1 (33.3)	4 (40.0)
Staphylococcus aureus	3 (11.1)	0	3 (33.3)	0	0	0
MRSA	2 (7.4)	1 (33.3)	0	0	0	1 (10.0)
CONS	2 (7.4)	0	0	1 (50.0)	0	1 (10.0)
Enterococcus	2 (7.4)	1 (33.3)	1 (11.1)	0	0	0
Klebsiella	2 (7.4)	0	1 (11.1)	0	0	1 (10.0)
Acinetobacter baumannii	4 (14.8)	0	2 (22.2)	0	1 (33.3)	1 (10.0)

The values are expressed as n (%) or [a]median (IQR). 1 case of each Pneumococcus, Burkholderia cepacia and Mycobacterium tuberculosis was isolated in group of antibody deficiency, phagocytic defect and innate immunity defect. AEFI: Adverse event following vaccination, MRSA: Methicillin-resistant Staphylococcus aureus, CONS: Coagulase negative Staphylococous

combined immunodeficiency with syndromic features (11.1%) and defect in innate immunity (11.1%). The commonest disorder in antibody deficiency group (n = 10) was common variable immunodeficiency (n = 6) followed by selective IgA deficiency (n = 3) and X-linked agamma-globulinemia (XLA) (n = 1). In the phagocytic function defect group, chronic granulomatous disease (CGD) was the commonest (n = 7), followed by Chediak-Higashi syndrome (n = 1) and LAD-1 deficiency (n = 1). In the combined immunodeficiency group, we found two cases of severe combined immunodeficiency (SCID). In immunodeficiency with syndromic features, we had two children with hyper IgE syndromes and one with Wiskott-Aldrich syndrome (WAS). Amongst the defects of innate immunity, we found two cases of Mendelian susceptibility to mycobacterial diseases (MSMD) and one natural killer (NK) cell deficiency. Overall, CGD was the commonest (25.9%) immunodeficiency seen in the study group. Follow-up at the end of 3 months included 20 out of 27 children, repeat tests were consistent with the preliminary diagnosis in all of them. Of the remaining seven children, 4 patients (2 SCID, 1 X-linked agammaglobulinemia, 1 CGD) died, and three were lost to follow-up.

Clinical presentation in terms of system wise involvement was assessed in PID subgroups (**Fig. 1**). Facial dysmorphism was present in two patients (7.5%), *viz*, low set ears in SCID and coarse facies in hyper IgE syndrome. Skin lesions present in 11 patients (40.74%) included hypo-pigmented areas (WAS), noma (SCID), hyperkeratosis (hyper IgE syndrome), vesiculobullous lesion, pyoderma and healed scars (CGD) and non-healing ulcers with sinus formation in MSMD. Twelve patients (44.44%) had deep seated abscesses and 14 (51.85%) had organomegaly. Six (22.22%) children presented with gastrointestinal complaints with most of them having a history of recurrent diarrhea and one child with WAS had blood mixed stools. Out of 17 children with respiratory complaints (62.9%), recurrent pneumonia was the commonest (n = 8, 47.05%) followed by lung abscess. Meningitis was present in four (14.8%) and one child had pyopericardium. Although blood cultures were sent in all cases, 17 children had a blood culture positive septicemia, the commonest pathogens being A*cinetobacter baumannii* and methicillin resistant *Staphylococcus aureus*. Around 88.8% children with phagocytic defects had a culture-positive sepsis.

Immunodeficiency with syndromic phenotypes had an older age at presentation (96 mo) when compared with children with phagocytic defects who presented at a median (IQR) age of 4 (3.0-11.0) mo. Hospitalization was more frequent among the syndromic patients. Both the children who were found to have SCID had a history of similar illness in the family.

Fig. 1 Clinical presentation in primary immunodeficiency diseases subgroups

DISCUSSION

In the current study, most of our patients had a history of multiple hospital admissions. However, with increased awareness, 70% of cases were detected below one year age and 14% were picked up after the first and second hospital admission. Similar experiences were found with other researchers too [4]. Three major Indian centers have reported their experience with cohorts of PID patients [4,5]. In late 2020s, similar reports were published from tertiary centers of Kerala and Karnataka [6,7].

In a study from Postgraduate Institute of Medical Education and Research, Chandigarh, antibody deficiency was the commonest (41.9%) PID, while at All India Institute of Medical Sciences, New Delhi and the National Institute of Immunohematology, Mumbai, it was seen in 18% and 15.5% of PIDs respectively. A global study by JMF reported a higher prevalence of 51.6% [8]. The proportion of children with phagocytic defects was comparable across the country (27-33%). Only 8% had a combined T and B cell defect, consistent with figures of 10-15% reported in other studies from India [5,7]. Varied observations may be attributed to a lack of awareness and diagnostic facilities, severity of disease, referral bias, genetic constitution of the citizens/inhabitants, rate of consanguineous marriages and many unknown factors.

Our cohort showed a prevalence of PID of around 93.24 per 100,000 hospitalized children, which is much higher compared to other countries, having reported prevalence of 5-30 PID cases every 100,000 populations [9-11]. Ours is a hospital-based study, contrary to other population-based studies. The difference in study recruitment might have contributed to such conflicting result. Recruitment of cases were done using the ten criteria proposed by the JMF which recently has shown to under diagnose PIDs and extended criteria have been proposed since then [12]. In the absence of nationwide data on PID prevalence in India, at least one million children are estimated to be suffering from PIDs by statistical projections [5]. Ours is the first study of this kind from eastern India wherein, the incidence of PIDs in hospitalized pediatric population was assessed prospectively and found to be about one per thousand hospital admissions. As published previously [13-16], parental consanguinity and relevant family history did seem to influence PID in our study too.

The current study highlights the issue of suspecting PIDs in situations where clinical conditions fulfill the JMF warning signs criteria. The limitation of our study is absence of long term follow up. Molecular study was not feasible due of the financial constraints. However, the current study highlights that clinical awareness, simple

WHAT THIS STUDY ADDS?

- Primary immunodeficiency disorders are not as rare as previously thought to be, if suspected cases are appropriately investigated.

blood count and few basic tests are enough to suspect the possibility of a PID.

Ethical clearance: Institutional Ethical Committee, Ref. no RKC/721, dated Feb 21, 2018.
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ORIGINAL ARTICLE

Pituitary Stalk Interruption Syndrome: Analysis of Response to Growth Hormone Therapy

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ABSTRACT

Objective: To analyse the clinical and radiological characteristics of pituitary stalk interruption syndrome (PSIS).

Methods: A retrospective analysis of confirmed cases of PSIS was performed. The development of new pituitary hormonal deficiencies and response to recombinant human growth hormone (rhGH) therapy were assessed during follow-up.

Results: This study included 14 children (10 boys) of PSIS with median (range) age of 12.15 years (2 months - 18 years). Short stature was the most common presentation (n = 13), and micropenis (n = 4), cleft lip (n = 1) and single central incisor (n = 1) were other midline defects. Growth hormone (GH) deficiency was present in 14 children and 7 of them also had multiple pituitary hormone deficiencies at baseline. Central hypothyroidism (n = 5), secondary adrenal deficiency (n = 4) and gonadotropin deficiencies (n = 2) were also seen. All children received rhGH. The mean height gain on follow-up was 12.78 cm in first year (n = 14), 6.5 cm in second year (n = 8) and 4.07 cm in third year (n = 7) of rhGH therapy. Four children developed additional pituitary hormone deficiency on follow-up.

Conclusion: Short stature with isolated GH deficiency was the most common presentation of PSIS that showed good response to rhGH therapy.

Keywords: *Midline defects, Multiple pituitary hormone deficiencies, Radiological features*

INTRODUCTION

Pituitary Stalk Interruption Syndrome (PSIS) is a radiological diagnosis, characterized by a constellation of a thin or absent pituitary stalk, an ectopic posterior pituitary, and a hypoplastic or aplastic anterior pituitary gland [1]. The incidence of PSIS is one in 2,00,000 births [2]. The etiology is multifactorial and postulated to be associated with genetic factors, and perinatal injury. PSIS could result after injury or anoxia of the pituitary stalk during breech delivery [3]. A mutation of the genes involved in pituitary development (*PIT1, PROP1, LHX3/ LHX4, PROKR2, OTX2, TGIF,* and *HESX1*) may also play a role [4].

The clinical presentation of PSIS depends on the age and number of pituitary hormone deficiencies. PSIS is associated with various midline defects like cleft lip, cleft palate, optic nerve hypoplasia, midline congenital anomalies of the brain, micropenis and corpus callosum agenesies. Children with multiple pituitary hormone deficiencies (MPHD) usually present in the neonatal period with hypoglycemia, prolonged jaundice, micropenis and failure to thrive. However, the most common presentation of PSIS during childhood is short stature and children usually are diagnosed in the first decade. Posterior pituitary dysfunction is rare.

There are a few studies of PSIS from India but no longitudinal study has assessed the response to recombinant human growth hormone (rhGH) therapy. This observational study aimed to assess the clinical, radiological and hormonal characteristics of PSIS and the response to rhGH therapy.

METHODS

This study analyzed the records of diagnosed cases of PSIS who presented to a tertiary care center in India between 2017 to 2022. The children having pituitary hormone deficiencies due to other causes (both congenital and acquired) were excluded.

Magnetic resonance imaging (MRI) of pituitary and brain were done using a 1.5 Tesla machine. The MRI criteria to diagnose PSIS included: pituitary height < 3.5

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mm and volume < 150 mm^3, pituitary stalk hypoplasia with anterior posterior (AP) diameter < 2.5 mm at the optic chiasma level [5,6], and ectopic posterior pituitary.

Growth hormone deficiency (GHD) was diagnosed if GH levels were < 10ng/mL on two stimulation tests (clonidine and glucagon) on two different days. Priming with sex steroids was done if the child's age was more than ten years in girls and more than eleven years in boys. Complete or severe GHD was defined as peak GH level below cut-off of 5 ng/mL. Secondary hypothyroidism (T_4 deficiency) was diagnosed by the presence of inappropriate TSH response (low, normal, or mildly elevated) to low T4 levels. Secondary adrenal insufficiency was diagnosed if baseline cortisol below 4µg/dL or ACTH-stimulated cortisol was below 20 µg/dL after one hour of 250 µg of intramuscular tetracosactide injection and low or normal ACTH. Pubertal staging was done using Tanner staging. Gonadotropin deficiency was diagnosed by the absence of pubertal changes by age of thirteen years in girls and fourteen years in boys and was confirmed by leuprolide-stimulated leutinising hormone (LH) levels below 5 mIU/mL following four hours of subcutaneous Leuprolide (dose of 20 µg/kg) injection. Hyperprolactinemia was diagnosed by prolactin levels of more than 20 ng/mL in both males and females. All the hormone levels were tested in Roche Cobas e411 using the electrochemiluminescent assay method.

Height (or length) were measured using stadiometer in children aged more than two years (or infantometer for children below two years of age) with an accuracy of 1 mm and an average of three readings was taken. Short stature was defined as height below 2 standard deviation (SD) from the mean for that child's age and sex. Micropenis was defined as stretched penile length below 2.5 SD from the mean for the corresponding age [7]. Cryptorchidism was identified clinically by the absence of testis in normal scrotal position. A thorough history of antenatal period, breech delivery and perinatal hypoxia requiring oxygen support were taken.

Children with short stature were started on rhGH at a dose of 0.16 mg/kg/week and the dose was titrated according to the clinical and insulin-like growth factor 1(IGF1) response. The other hormone deficiencies were treated with age-appropriate dosages of necessary hormone replacement. The follow-up records of the children were collected for the annual height gained per year and pubertal development. Assessment was performed every three to six monthly, both clinically and biochemically, for the development of any new hormonal deficiencies.

Statistical analysis: Data were analyzed using XLSTAT software for Microsoft Excel 21. Descriptive data were expressed in terms of mean (SD), median (range), and percentages. Student's *t*-test was used for continuous variables. *P* value of less than 0.05 was considered to be statistically significant.

RESULTS

A total of 14 children (10 boys) were included in this study with a median (range) age of presentation of 12.15 years (2 months-18 years). The most common presentation was short stature (*n* = 13). One child was diagnosed with hypoglycemic seizures in infancy. Breech delivery was documented in 5 cases and 4 patients had perinatal hypoxia requiring oxygen support. Midline defects were seen in six children (**Table I**). The hormonal work-up is shown in **Table I.**

Only seven children had two or more anterior pituitary hormone deficiencies (multi-pituitary hormone deficiency, MPHD). Hyperprolactinemia (5/7) and midline defects (5/7) were seen in children with MPHD. Among the radiological features, anterior pituitary hypoplasia (*n* = 14), stalk thinning (*n* = 9), ectopic posterior pituitary bright spot (PPBS) (*n* = 11), and absent PPBS (*n* = 3) were seen. The mean anterior pituitary height was 2.86 mm and width of the stalk was 1.52 mm. The location of the ectopic PPBS was in the median eminence (*n* = 4) or infundibulum (*n* = 7). There were no intracranial midline abnormalities.

During follow-up, newer pituitary hormone deficiencies developed in 4 children (central hypothyroidism in

Table I Baseline Characteristics of Children With Pituitary Stalk Interruption Syndrome (*n*=14)

Baseline characters	*Values*
Height-for-age *Z* score[a]	-5.28 (1.87)
Bone age[a](y)	6.77 (1.93)
Bone age delay[a] (y)	4.99 (1.83)
IGF1 (ng/mL) [a]	47.44 (29.72)
GH (ng/mL) [a]	1.21 (0.30)
Breech delivery, *n*	5
Perinatal hypoxia, *n*	4
Midline defects, n	
Micropenis	4
Cleft lip	1
Single central incisor	1
Anterior pituitary hormone functions, n	
GH deficiency	14
Central hypothyroidism	5
Central adrenal insufficiency	4
Central hypogonadism	2
Hyperprolactinemia	5

[a]*Data expressed as mean (SD); n =13 (excluding one infant)*

WHAT THIS STUDY ADDS?

- Children with pituitary stalk interruption syndrome manifest with growth hormone deficiency and may develop additional pituitary hormone deficiencies on follow-up.

two, secondary adrenal insufficiency in one and gonadotropin deficiency in one). The mean height gain on rhGH therapy was 12.78 cm in the first year of treatment (n = 14). 6.5 cm in second year (n = 8), and 4.07 cm in the third year (n = 7). At the end of 12 months, there was a significant increase in mean (SD) height SDS from -5.28 (1.87) to -3.66 (1.44) (P < 0.001). The mean (SD) IGF1 levels increased from 47.4 (29.7) to 285.7 (97.1) ng/mL (P < 0.001) after one year follow-up. The mean dose of rhGH was 0.21 mg/kg/week at the end of first year.

DISCUSSION

The present study reports clinical and biochemical characteristics in children with PSIS treated with rhGH. PSIS is a rare cause of short stature and mostly presents in the first decade of life with a male preponderance [8]. The median age of presentation in this study, suggested a later presentation, probably due to a lack of awareness of this condition. Children with PSIS present with variable degrees of complete or partial anterior pituitary hormones deficiencies. Short stature was the most common presentation with GHD as was also seen earlier [9]. Hyperprolactinemia was seen in 33-45% of PSIS cases earlier [9,10], similar to this study. Hyperprolactinemia depends on the degree of dopaminergic pathway disconnection. Children in this study did not have central diabetes insipidus (DI) with ectopic or absent PBBS, the exact cause of which is not known. A few studies have reported DI in PSIS due to osmo-receptor dysfunction [11]. A similar study from India on 14 pateints with PSIS reported a male preponderance, breech presentation, and external congenital anomalies to be common in PSIS while DI was rare [12].

In the present study, hyperprolactinemia and the presence of midline defects were associated with MPHD as also seen earlier [13]. Breech delivery was seen in approximately one-third of the children in this study, similar to 45-89% reported in other studies on PSIS [9, 14], that is higher than the population rate of 5%.

The response to rhGH therapy was good with maximum height gain in the first year of therapy, similar to other studies with a first year height gain of approximately 9 cm [10,15]. The detection of additional pituitary hormone deficiencies during follow-up suggests the need of regular monitoring of anterior pituitary hormone deficiencies. The limitations of this study were small sample size, limited follow-up period and absence of confirmatory genetic testing.

To conclude, PSIS is a rare complex disorder with multi-factorial causes and varied presentation. These patients require hormone replacement therapies throughout lifetime and should be evaluated periodically for the development of additional hormone deficiencies.

Ethical clearance: Institute Ethics Committee, Gauhati Medical College; No. MC 190/2007/Pt-II/April-2023/17, dated June 23, 2023.
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SYSTEMATIC REVIEW

Effect of Splint Application on the Functional Duration of Peripheral Intravenous Cannulation in Neonates: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The application of splints is one of the most used methods to prolong the life span of peripheral intravenous cannulation (PIVC).

Objective: To assess the effect of splint application on the functional duration of PIVC in neonates.

Methods: This systematic review and meta-analysis identified, appraised, and synthesized available evidence from randomized and quasi-randomized controlled trials (RCT) related to the effects of splint application compared to no splinting on the functional duration of PIVC and its associated complications in term and preterm neonates. Data were pooled using RevMan 5.4. The quality of evidence for predefined outcomes was analyzed by GRADE.

Results: Available evidence (5 RCTs, 826 neonates) showed a significantly lesser functional duration of PIVC in the splint group compared to no-splint [Mean Difference (MD) 95% Confidence Interval (CI) -3.07 (-5.63, -0.51); Low Certainty of Evidence (CoE)]. On gestation-based subgroup analysis, PIVC duration remained significantly lesser in the splint group in preterm neonates [MD (95% CI), -5.09 (-9.53, -0.65), 2 studies, *n* = 220; Low CoE], whereas it was comparable in the term neonates [MD (95% CI), 3.92 (-4.27, 12.10), 2 studies, *n* = 89; Very low CoE]. The overall complications were comparable between the groups [Risk Ratio (95% CI), 1.02 (1.00, 1.05), 5 studies, *n* = 826; Very low CoE].

Conclusions: Based on the very low to low CoE found in this systematic review, it is not possible to recommend or refute splint application in neonates. Further well-designed RCTs are needed.

Keywords: *Complications, Newborn, Venous access*

Protocol Registration: PROSPERO database (CRD42023431871) ***Published online:*** Jan 09, 2024; ***PII:*** S097475591600585

INTRODUCTION

Peripheral intravenous cannula (PIVC) insertion is one of the most performed procedures in neonatal intensive care units (NICU) [1]. It is a relatively fast method to achieve intravenous (IV) access to deliver medications, blood products and parenteral nutrition in hospitalized neonates [2]. Prospective observational studies report an average functioning longevity of PIVC ranging from 24 to 48 hours [3]. Maintaining cannula patency for a longer duration is often challenging. Repeated attempts for IV cannulation are painful and often result in immediate cardio-respiratory instability in sick neonates [4]. Moreover, multiple pricks increase the incidence of sepsis, raise the cost of care, and may even adversely affect long-term neurological outcomes [5].

Several interventions have been studied to prolong the life span of PIVC. The application of a splint to immobilize the adjacent joints is one of the most used methods [1]. Several randomized controlled trials (RCT) have evaluated the effect of splints on PIVC duration in neonates, but the results are conflicting [6-10]. A splint has the potential to increase the duration of cannula patency by preventing the kinking of the catheter and its inadvertent removal [11]. On the contrary, splinting may increase local complications by compressing the fragile skin and masking the signs of inflammation and infiltration [12]. Moreover, the adhesive material used for

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splint application may lead to allergic skin reactions as well [13]. This systematic review and meta-analysis were conducted to identify, appraise and synthesize available evidence related to the effects of splint application compared to no splinting on the functional duration of PIVC in neonates, to guide the present practice and plan for future research.

METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration number CRD42023431871) [15].

Objectives

The primary objective was the functional duration of PIVC in neonates with and without the application of a splint. Secondary objectives were the comparison of the same in the subgroups of the term (gestational age, GA ≥37 week) and preterm (GA<37 week) neonates, splinting in relation to the joints, nature of infusion (continuous/intermittent) and the incidence of PIVC-related adverse events.

Inclusion and exclusion criteria

RCTs and quasi-RCTs, published in English, with term and/or preterm neonates as participants, assessing the effects of splint application as an intervention, compared to no-splint application, as a comparator, on the functional duration of PIVC were included. Non-English publications and conference abstracts were excluded.

Outcome measures

The primary outcome measure was the functional duration of PIVC (hours). Secondary outcome measures included the functional duration (h) in the pre-specified sub-groups and the incidence of PIVC-related adverse events such as infiltration, phlebitis, extravasation, blockage/occlusion, inflammation, leakage, erythema, palpable cord etc.

Search strategy

Different databases including PubMed, Embase, Cochrane Central, CINAHL, Google Scholar, Scopus, Web of Science, and different clinical registries were searched by two authors independently from inception till May 2023 for peer-reviewed articles published in English. A combination of free text keywords and their representative controlled vocabulary terms using appropriate Boolean operators was used to formulate the electronic search strategy in different databases (**Table I**). Two authors screened each record independently for possible inclusion in the systematic review. Disagreement, if any, was resolved by discussion among all the authors. The full text of all articles was also checked to find additional articles.

Data extraction

The study details and outcome data were collected by two authors independently in a pre-designed dataset. Study details collected included the year and the place of study; inclusion and exclusion criteria and other methodological details, features of the PIVC and the splint used, the procedure, characteristics of the participants in the intervention and control arm, and the reported outcomes.

Assessment of risk of bias (RoB)

RoB for each study was assessed by all authors independently as per the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [16]. Disagreements were resolved by discussion and consensus among the review authors.

Statistical analysis: Statistical analysis was performed using Review Manager version 5.4 [17]. Reported outcomes including mean and standard deviation (SD) and the proportions were pooled for meta-analysis. Mean difference (MD) and 95% confidence intervals (CI) were

Table I Details of Database Search

Database	*Date*	*Search Strategy*	*Number of references*
PUBMED *https://www.ncbi.nlm.nih.gov/pubmed/*	01-07-2023	(((Infant, Newborn) OR Intensive Care Units, Human, Neonatal, AND (Cannula* OR Catheterization OR Peripheral / methods* OR Peripheral* / adverse effects, Joints* OR Infusions, Intravenous)) AND (Splints*) OR Restraint, Physical*) AND (Treatment Outcome)	494
EMBASE *https://www.embase.com/*	01-07-2023	((newborn OR infant) AND cannula OR catheterization OR peripheral) AND splint AND functional duration OR 'treatment outcome'	447
CENTRAL *https://www.cochranelibrary.com/*	01-07-2023	"newborn infant" OR neonatal intensive care unit in Title Abstract Keyword AND cannula* OR Catheterization OR Peripheral in All Text tAND splint*	2

calculated for different outcome variables. A risk ratio (RR) with 95% CI was calculated for dichotomous data. Heterogeneity was assessed using the I^2 statistics. We planned to assess the publication bias by funnel plot and Egger test, if the number of included studies was more than 10. A sensitivity analysis was planned for the studies that used commercial splints. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [18] was applied to assess the Certainty of Evidence (CoE) for the predefined outcomes. A table of summary of findings was generated on the GRADEpro GDT software [19].

RESULTS

Search results

A total of 951 articles were identified from different databases based on the previously mentioned search strategy. After removing the duplicates, the title and abstract of 228 studies were screened. Full texts of nine articles were read of which four were excluded [20-23]. Finally, 5 RCTs [6-10], recruiting a total of 826 neonates, were included in this meta-analysis. PRISMA flow diagram was shown in **Fig. 1**. Details of excluded studies were summarized in **Web Table I**.

Included studies

Table II summarizes the characteristics of the included studies. All studies were carried out in India. Splint and no-splint groups were comparable with respect to their GA [7-10] and birth weight (BW) [6,8-10]. All of the studies used 24-gauge (G) PIVC, whereas two studies [7,10] used 26G as well. Veins selected for an attempt of cannulation and the nature of infusate were pre-specified and comparable in intervention and control arms in all studies. The age of PIVC insertion was mentioned in two studies [9,10], and both groups had comparable distribution. The procedure was done by doctors/nurses [6,7,9,10]. Tewari et al [8] did not mention the person performing the procedure. Only one study used extension tubing [9]. Three studies used commercially available splints [8-10]. The size of the splint and the method of fixation were standardized in three studies [6,9,10]. Three studies used syringe pumps for the delivery of IV fluids and medications [6,7,10]. Others did not mention the method of delivery. Though PIVC-related complications were pre-defined by all authors, only two studies [7,10] used the standard definitions given by the Infusion Nurse Society [24]. Regular monitoring for the detection of complications was done in 3 studies [8-10]. Except for the splint, other interventions were similar in all the included trials in both arms.

RoB Assessment

Only one study was prospectively registered in the Clinical Trial Registry [10]. A-priori sample size calculation was done in three studies [6,9,10]. RoB for each included study is summarized in **Fig. 2A**. **Fig. 2B** depicted RoB graph

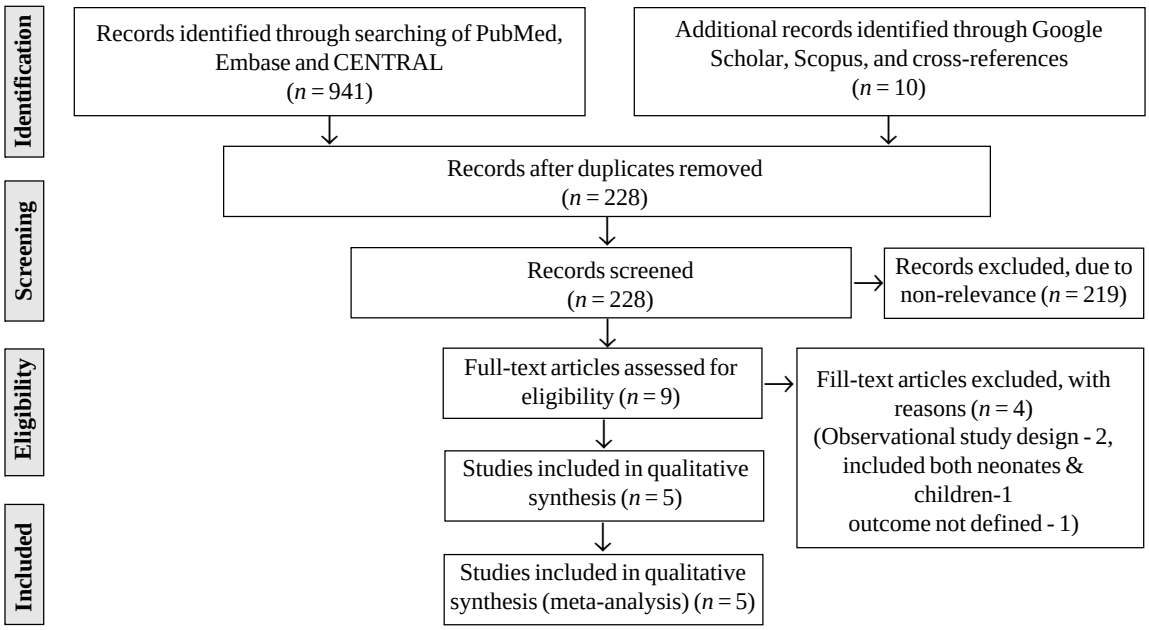

Fig. 1 PRISMA flow diagram

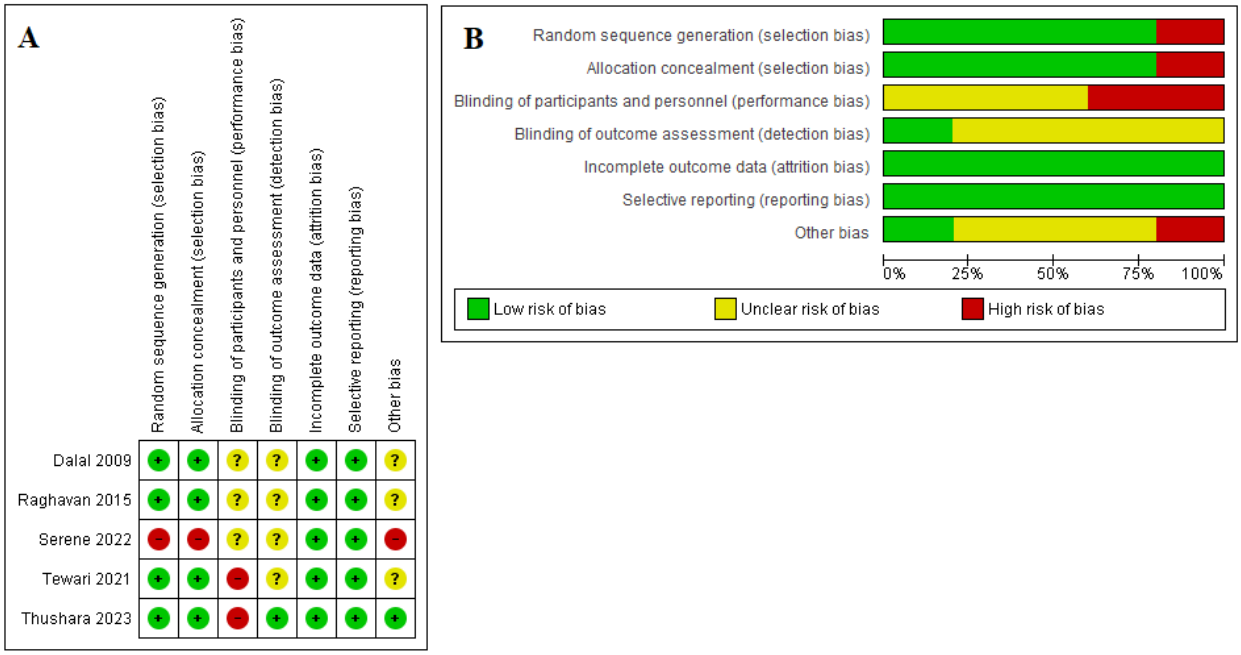

Fig. 2 A Risk of bias for each included study, **2B** Each Risk of bias item as percentages across all studies

summarizing each RoB item as percentages across all studies.

Outcome variables

All outcomes were reported in the same unit in all the studies. There were no missing data.

Functional duration of PIVC (Fig. 3)

All five studies have reported the primary outcome. After pooling the data, the functional duration of PIVC in the splint group was significantly less compared to the no-splint group [MD (95% CI), -3.07 (-5.63, -0.51), I^2 = 0%, 5 studies, *n* = 826; Low CoE] (**Fig. 3A**).

On gestational sub-group analysis, there was no significant difference between the splint and no-splint groups in the term population [MD (95% CI), 3.92 (-4.27, 12.10), I^2 = 38%, 2 studies, *n* = 89; Very low CoE] (**Fig. 3B**). However, in preterm neonates, the functional duration was significantly less in the splint group [MD (95% CI), -5.09 (-9.53, -0.65), I^2 = 0%, 2 studies, *n* = 220; Low CoE] (**Fig. 3C**).

Data could not be pooled for other subgroups as only one study reported the outcome of splinting in relation to joints [9], and another single study reported the outcome with respect to the nature of infusion (continuous/ intermittent) [10].

On sensitivity analysis, pooling the data from studies that used commercial splints [8-10], significantly lesser duration was found in the splint group [MD (95% CI), -3.69 (-7.11, -0.27), I^2 = 0%, 3 studies, *n* = 371].

Incidence of PIVC-related complications (Fig. 4 A-D)

Pooled data from all 5 studies showed a high incidence of complications in both splint and no-splint groups without any significant difference [RR (95% CI), 1.02 (1.00, 1.05), I^2 = 77%, 5 studies, *n* = 826; Very low CoE]. Individual complications including blockage and inflammation were also comparable.

Summary of findings

Pooled CoE from the included studies was summarized using the GRADE approach in the summary of findings tables (**Table III**).

DISCUSSION

In the present systematic review, very low to low CoE found the functional PIVC duration to be significantly lesser by 3 hours in the splint group compared to no splint in neonates. On gestation-based subgroup analysis, PIVC duration remained significantly lesser in the splint group in preterm neonates by 5 h, whereas it was comparable in the term neonates. The overall complication, inflammation, and occlusion rates were comparable between the groups.

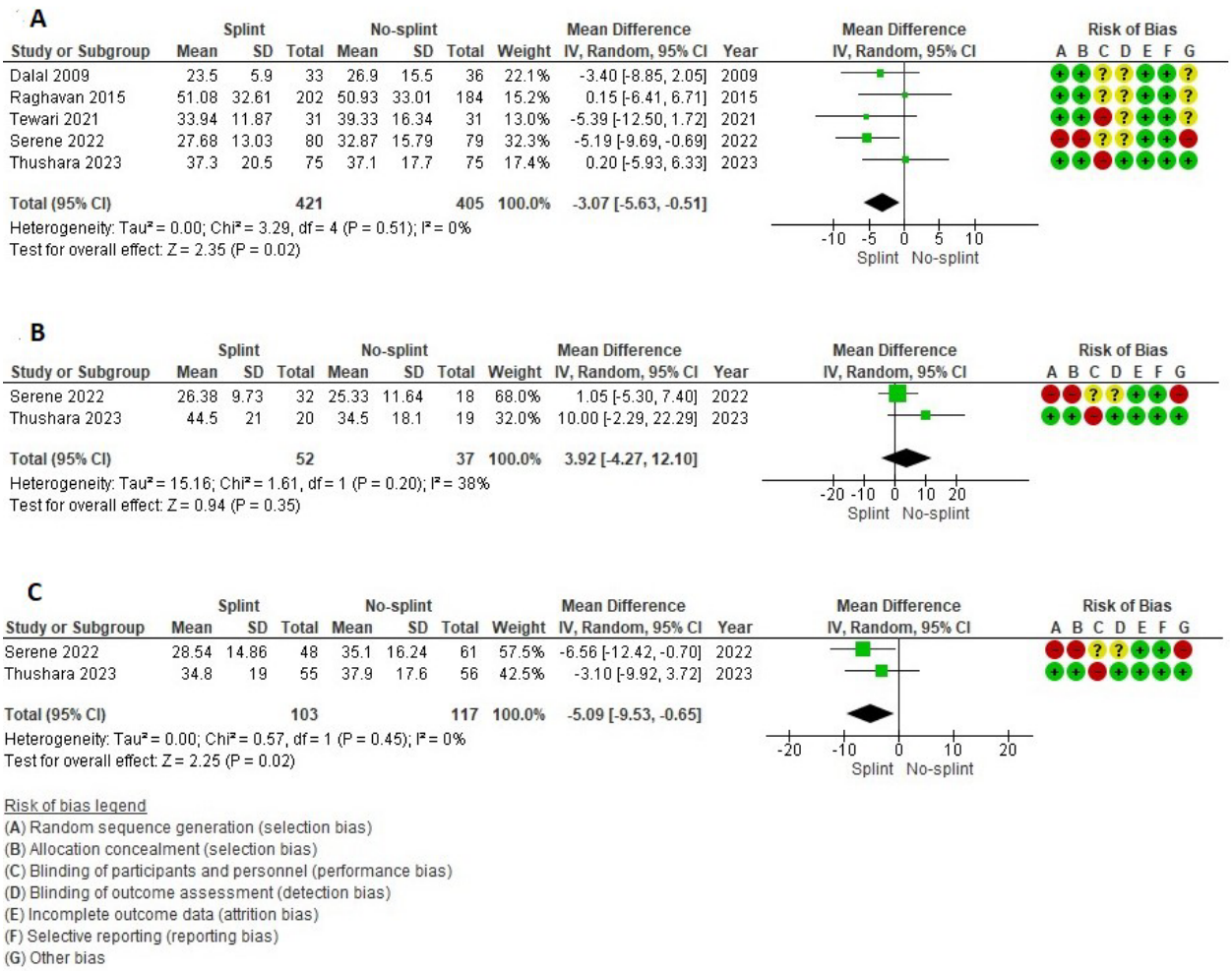

Fig. 3 Forest plots for the functional duration of peripheral intravenous cannula (PIVC); **3A** Overall; **3B** In term neonates; **3C** In preterm neonates.

Nursing society guidelines advocated the use of splints for PIVCs inserted near the joints [24,25] to prevent repeated joint flexion that may result in sudden elevation of pressure within the veins and cause microtrauma and inflammation to the tunica by catheter movement [25]. However, the present meta-analysis does not support this practice and found splint application to reduce the functional PIVC duration by 3-5 hours. Compression of the fragile veins by the adhesive tapes used to fix the splints could decrease the dwelling time of PIVC. On subgroup analysis, functional PIVC duration was significantly shorter in preterm neonates whereas it was comparable in term neonates. It may be postulated that splints may prolong PIVC duration in term neonates by restraining their actively moving extremities and better skin maturity could avoid splint-related adverse effects [10]. Moreover, restraining limbs for a longer period, especially in non-physiological positions may be uncomfortable for the neonate and result in muscle weakness [24]. PIVC patency remained significantly shorter even with the use of commercially available splints.

The primary outcome was reported by all authors, though the heterogeneity across the studies was variable. However, the studies were associated with a serious risk of bias, as blinding could not be done due to the nature of the intervention. The details of various factors that may potentially affect PIVC duration including BW and GA, postnatal age at catheter insertion, site and size of cannula placement, infusion rate, use of syringe pump, indication for IV treatment, type of infusion (continuous vs intermittent), and use of intermittent flushing with saline/heparin have not been addressed uniformly in the included studies. The variability of these factors along with the frequency and expertise of the health worker monitoring the complications might affect the reported outcomes.

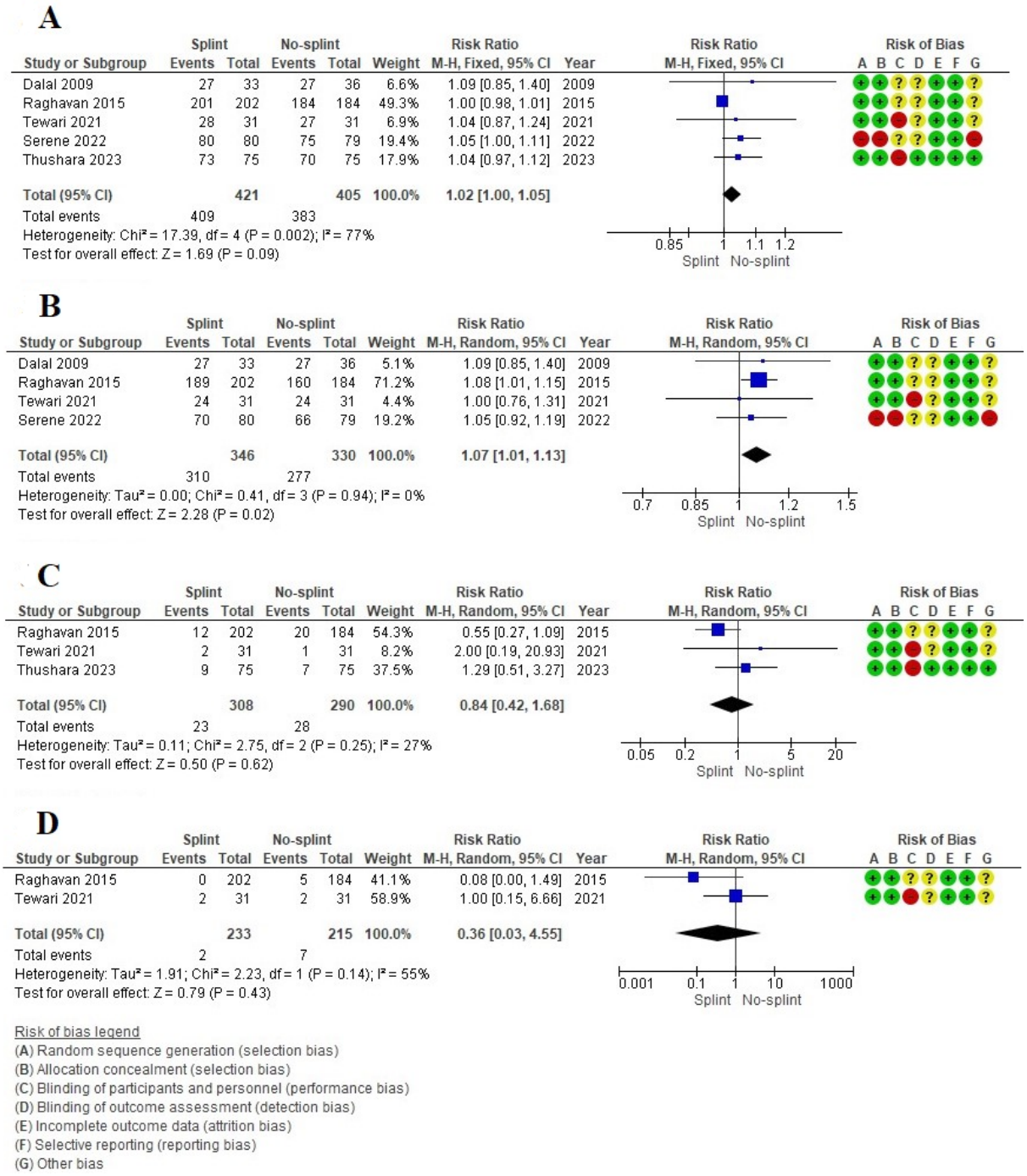

Fig. 4 Forest plots for the complications of peripheral intravenous cannula (PIVC); **4A** Any complication; **4B** Extravasation; **4C** Blockage; **4D** Inflammation

In all the studies, PIVC-related complication rates were high irrespective of the application of the splint except in the study by Raghavan et al [7] who reported significantly higher complications in the splint group. Only two of the included studies used standard definitions [7,10] to define PIVC-related complications. Differences in the definition of complications across the studies limited the pooling of the data. The need for prolonged IV therapies, especially in preterm and sick neonates, and removal of PIVC only after developing

Table II Characteristics of Included Studies

Study description	*Dalal et al* [6]	*Raghavan et al* [7]	*Tewari et al* [8]	*Serene et al* [9]	*Thushara et al* [10]
Location	India	India	India	India	India
Study period	NM	March 2015 - July 2015	May 2011 – July 2011	NM	Sept 2021 to Sept 2022
Year of publication	2009	2015	2021	2022	2023
Methods					
Study type	RCT	RCT	RCT	RCT	RCT
Registered	NM	NM	NM	NM	Yes
Inclusion criteria	Preterm and termneonates anticipatedto require PIVC infusion for at least > 72 h	Preterm and termneonates anticipatedto require PIVC infusion for at least > 48 h	Preterm and termneonates anticipatedto require PIVC infusion for at least > 48 h	Preterm and term neonates anticipated to require PIVC infusion for at least > 24 h	Preterm and termneonates anticipatedto require PIVC infusion for at least > 24 h
Exclusion criteria	Major congenital malformations	NM	Major congenital and limb anomalies; Failure to obtain consent; Newborns with central venous catheter	Requirement of multiple simultaneous PIVC access, elective removal of PIVC within 6 h, indwelling central vascular catheters	Congenital anomalies affecting the limbs; Prior cannulation at the same site
Sample size	69 cannulations in 54 neonates	386 cannulations	62	159	150 cannulations
A-priori sample size calculation (*n*)	Yes (36)	No	Yes (62)	Yes (156)	Yes (150)
Primary outcome variable	NM	The time from insertion of PIVC to development of predefined signs of cannula removal	Functional longevity of the PIVC (h), from the time of inser tion to the time of removal	NM	Functional duration of PIVC (h) from the time of insertion to the time of development of signs of PIVC failure
Secondary outcome variables	NM	NM	NM	NM	Incidence of complications; Subgroup analysis was done in neonates with different GA (<32; 32-36 and ≥ 37 weeks) and the type of IV infusion (intermittent and continuous).
PIVC details					
Procedure done by	Senior (neonatology training fellows) and junior (pediatric residents)	Senior and junior residents, nurses	Senior residents and neo-natology fellows	Medical or nursing staff	Neonatology residents with NICU experience for > 1 year
Cannula size (G)	24	24 and 26	24	24	24 and 26

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Study description	*Dalal et al* [6]	*Raghavan et al* [7]	*Tewari et al* [8]	*Serene et al* [9]	*Thushara et al* [10]
Site	Wrist, elbow, knee, or ankle	Wrist, elbow, ankle	Wrist, elbow, knee or ankle, and forearm, or any other site in the limbs	Hand, forearm, foot and leg	Dorsum of the hands, foot, and cubital area
Material	Becton Dickinson India Pvt	BD Neoflon,	Polyurethane IV cannula (Vasofix®)	Vygonule V from Vygon	Polytetrafluoroethylene
Fixation technique	Standardized technique	Standardized technique	Standardized technique	3M TegadermTMI.V. Transparent Film Dressing	Secured with transparent tape, both the flanges of PIVC being secured by another tape maintaining clear visibility of skin at the site of PIVC insertion and its tip
Connector tubing	NM	NM	NM	Needleless catheter access device with 6 inches extension	NM
Infusion delivery through PIVC	Syringe pump	NM	Syringe pump	NM	Syringe pump
Type of medication	10% dextrose, 10% dextrose + calcium gluconate, N/5 in 10% dextrose, parenteral nutrition ($P > 0.05$)	Calcium	Dextrose 10%, partial parenteral nutrition, Isolyte P	Intermittent, continuous and parenteral nutrition	Parenteral nutrition, Calcium gluconate, Antibiotics
PIVC related complication definition	Defined by the authors	As per Infusion Nurse Society definition	Predefined by the authors	Predefined by the authors	As per Infusion Nurse Society definition
Monitoring for complications	2-hourly		2 -3 hourly	Dedicated observer reviewed the catheter sites regularly	2-hourly
Use of skeletal muscle relaxants,sedatives, and analgesics	No	NM	No	NM	NM
Intervention description					
Splint	Cotton and gauzepiece rolled over a hard cardboard piece	Firm splintcovered with a sterile gauze	Commercially available generic neonatal splint	Commercial splints made from cardboard and sponge	Commercially available flexible splints made up of soft polyurethane foam with an aluminum strip core (FLEXI-Board®, Respicare Solutions, Mumbai, India)

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Study description	*Dalal et al* [6]	*Raghavan et al* [7]	*Tewari et al* [8]	*Serene et al* [9]	*Thushara et al* [10]
Size	Length extending 2 inches on either side of the joint and width equal to the width of the limb just proximal to the joint	NM	NM	Standard size (3 × 2 inches)	Small size (Size S; 7 cm × 2.5 cm × 0.7 cm)
Method of splint fixation	Standardized	NM	NM	Fixed across jointsensuring that the splint was not too tight to obstruct theflow of fluids	Snugly fixed with transparent silicone adhesive tape (Sil-GRIP, Respicare solutions, Mumbai, India)
No-splint	Except for splint other interventions similar	Except for splint other interventions similar	Except for splint other interventions similar	Except for splint other interventions similar	Except for splint other interventions similar
Splint	Cotton and gauzepiece rolled over a hard cardboard piece	Firm splintcovered with a sterile gauze	Commercially available generic neonatal splint	Commercial splints made from cardboard and sponge	Commercially available flexible splints made up of soft polyurethane foam with an aluminum strip core (FLEXI-Board®, Respicare Solutions, Mumbai, India)
Size	Length extending 2 inches on either side of the joint and width equal to the width of the limb just proximal to the joint	NM	NM	Standard size (3 × 2 inches)	Small size (7 cm x 2.5 cm x 0.7 cm)
Method of splint fixation	Standardized	NM	NM	Fixed across jointsensuring that the splint was not too tight to obstruct theflow of fluids	Snugly fixed with transparent silicone adhesive tape (Sil-GRIP, Respicare solutions, Mumbai, India)
No-splint	Except for splint other interventions similar	Except for splint other interventions similar	Except for splint other interventions similar	Except for splint other interventions similar	Except for splint other interventions similar
Intervention/Control Group Comparisons					
	Splint (n = 33); No-splint Group (n =36)	Splint (n = 202); No-splint Group (n = 184)	Splint (n =31); No-splint Group (n =31)	Splint (n =80); No-splint Group (n =79)	Splint (n =75); No-splint Group (n =75)
Baseline characteristics					
Gestational age (wk), mean (SD)[a] or median (IQR)[b] or median	32 (30-33)[b]; 33 (31-35)[b]	Median (range) 36 (28-42)[c]	35.81 (3.06)[a]; 34.77 (3.07)[a]	28-40[d]	34.6 (4.6)[a]; 34.1 (3.9)[a]

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Study description	*Dalal et al* [6]	*Raghavan et al* [7]	*Tewari et al* [8]	*Serene et al* [9]	*Thushara et al* [10]
(range)[c] or range[d]					
GA distribution (wk) *n* (%)	NM	< 34 wk: 49 (24.3), late preterm: 99 (49), term:54 (26.7); < 34-36 wk: 36 (19.6), late preterm: 92 (50), term: 56 (30.4)	Preterm: 22 (70.9), term: 9 (29.1); Preterm: 25 (80.6), term: 6 (19.4)	<*34 wk: 30 (18.9), 35-36 wk: 18 (11.3), <*37 wk: 32 (20.1); <*34 wk: 49 (30.8), 35-36 wk: 12 (7.5), <*37 wk: 18 (11.3) ($P < 0.05$)	< 32 wk:11 (28.9), 32-36 wk: 14 (36.8), ≥ 37 wk: 13 (34.2); < 32 wk: 8 (24.2), 32-36 wk: 14 (42.4), ≥ 37 wk: 11 (33.4)
Birth weight (g), Mean (SD)[a] or median (IQR)[b] or median (Range)[e]	1226 (984-1511)[b]; 1131 (933-1352)[b]	1800 (750-4100)[e]	2110 (650)[a]; 1850 (660)[a]	1993 (921)[a]; 2150 (774)[a]	1801 (730)[a]; 1779 (664)[a]
BW wise distribution g*n* (%) (51.5),	NM	VLBW: 67 (33.2), LBW: 116 (57.4); VLBW: 116 (36.4) LBW: 90 (48.9)	NM	< 1500: 10 (6.3), 1500-2500g: 38 (23.9), > 2500g: 32 (20.1); < 1500g: 28 (17.6), 1500-2500g: 25 (15.7), >2500g: 26 (16.3) ($P < 0.05$)	< 1500g: 17 (44.7), 1500-2499g: 11 (28.9), ≥ 2500 g: 10 (26.4); < 1500g: 17 1500g: 2499g: 10 (30.3), ≥ 2500g: 6 (18.2)
Site distribution, *n* (%)	Wrist: 26 (79), others: 7 (21);Wrist: 26 (74), others: 10 (26)	Wrist: 184 (91.1), ankle: 16 (7.9), elbow: 2 (0.9); Wrist: 165 (89.6), ankle: 18 (9.8), elbow: 1 (0.5)	Wrist: 23 (74.1), ankle: 3 (9.6), elbow: 5 (16.1); Wrist: 21 (67.7), ankle: 2 (6.5), elbow: 8 (38.0)	Hand: 55 (34.6), forearm: 4 (2.5), foot: 14 (8.8), leg: 7 (4.4); Hand: 50 (31.4), forearm: 10 (6.3), foot: 10 (6.3), leg: 9 (5.7)	Wrist: 50 (66.7), elbow: 3 (4.0), foot: 22 (29.3);Wrist: 36 (48.0), elbow: 6 (8.0), foot: 33 (44.0)
Age of PIVC insertion (days), mean (SD)[a] or median (IQR)b	NM	NM	NM	2.59 (1.61)[a]; 3.32 (1.71)[a]	4 (1-9)[b]; 4 (2-11)[b]
Procedure done by *n* (%)	Nurses: 2 (6), senior residents: 19 (58), junior residents: 12 (36); Nurses: 0, senior residents: 22 (63), junior residents: 13 (37)	Nurses: 151 (74.6), residents: 51 (25.2); Nurses: 146 (79.3), residents: 38 (20.7)	NM	Doctor: 17 (10.7), senior staff nurse: 57 (35.8), staff nurse:6 (3.8);Doctor: 39 (24.5), senior staff nurse: 31 (19.5), staff nurse: 9 (5.7) ($P < 0.05$)	Neonatology residents with experience of working in the NICU for over one year
Type of IV fluid, *n* (%)	PN: 9 (29), calcium:13 (37); PN: 6 (17), calcium: 13 (37)	Calcium: 75 (37.1); Calcium: 48 (26.1)	Dextrose 10%: 19 (61.2), partial PN: 12 (38.7) Isolyte *P*: 0; Dextrose 10% - 16 (51.6) , partial PN: 14	Intermittent: 3 (1.9), continuous: 77 (48.4), PN: 0; Intermittent: 2 (1.3), continuous: 70 (44.0), PN: 7 (4.4)	Continuous infusion: 59 (78.7), intermittent infusion: 16 (21.3); Continuous infusion: 56 (74.7), inter-

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Study description	*Dalal et al* [6]	*Raghavan et al* [7]	*Tewari et al* [8]	*Serene et al* [9]	*Thushara et al* [10]
			(45.2), Isolyte P: 1 (3.2)		mittent infusion: 19 (25.3)
Calculated outcomes					
Duration of PIVC, h, mean (SD)[a] or median (IQR)[b]	23.5 (5.9)[a];26.9 (15.5)[a] *P* = 0.38	51.08 (32.61)[a]; 50.93 (33.01)[a] *P* = 0.807	33.94 (11.87)[a];39.33 (16.34)[a] *P* = 0.14	27.68 (13.03)[a];32.87 (15.79)[a] *P* = 0.03	28.0 (23.0-48.0)[b]; 30.0 (25.0 -48.0)[b] *P* = 0.477
Duration of PIVC in preterm, h, mean (SD)	NM	NM	NM	*n* = 48, 28.54 (14.86); *n* = 61, 35.10 (16.24)*P* = 0.03	*n* = 55, 34.8 (19); *n* = 56, 37.9 (17.6) *P* = 0.735
Duration of PIVC in term, h, mean (SD)	NM	NM	NM	*n* = 32, 26.38 (9.73); *n* =18, 25.33 (11.64) *P* > 0.05	*n* = 20, 44.5 (21); *n* = 19, 34.5 (18.1) *P* = 0.177
Duration of PIVC across joints, h, mean (SD)	NM	NM	NM	26.07 (13.38); 28.49 (12.89) *P* = 0.436	NM
Duration of PIVC in continuous infusion group, h, median (IQR)	NM	NM	NM	NM	28 (22-48); 30.5 (26-48) *P* = 0.307
Duration of PIVC in intermittent infusion group, h, Median (IQR)	NM	NM	NM	NM	34.5 (25 - 47.5);26 (24-46) *P* = 0.515
Infiltration, *n* (%)	NM	NM	NM	NM	38/75 (52.1); 41/35 (58.5) *P* = 0.433
Phlebitis, *n* (%)	NM	NM	NM	NM	43/75 (58.9); 36/75 (51.4) *P* = 0.369
Extravasation, *n* (%)	27/33 (84); 27/36 (76.5) *P* > 0.05	189/202 (93.6); 160/184 (86.9) *P* < 0.05	24/31 (77.4); 24/31 (77.4) *P* = 1.00	70/80 (44); 66/79 (42) *P* > 0.05	NM
Blockage, *n* (%)	NM	12/202 (5.9); 20/184 (10.8) *P* < 0.05	2/31 (6.5); 1/31 (3.2) *P* = 1.00	NM *P* =0.658	9/75 (12.3); 7/75 (10.0)
Inflammation, *n* (%)	NM	0/202 (0); 5/184 (2.7) *P* < 0.05	2/31 (6.5); 2/31 (6.5) *P* = 1.00	NM	NM
Leakage, *n* (%)	NM	NM	0;0	NM	NM
Erythema, *n* (%)	NM	NM	NM	11/80 (13.8); 7/79 (8.9) *P* > 0.05	NM
Palpable cord, *n* (%)	NM	NM	NM	3/80 (3.8); 2/79 (2.5) *P* > 0.05	NM
Any complications, *n* (%)	27/33 (84); 27/36 (76.5) P > 0.05	201/202 (99.5); 184/184 (100) *P* = 1.00	28/31 (90.3); 27/31 (87.0) *P* = 1.00	80/80 (100); 75/79 (94.9) *P* = 0.704	73/75 (97.3); 70/75 (93.3) *P* = 0.441

BW: birth weight, GA: gestational age, h: hour, IQR: interquartile range, LBW: low birth weight, n: number, NM: not mentioned, PIVC: peripheral intravenous cannula. RCT: randomized controlled trial, SD: standard deviation, VLBW: very low birth weight, Wk: week

Table III GRADE Summary of Findings for Splint Compared to No-splint for the Functional Duration of Peripheral Intravenous Cannulation

Patient or population: Neonates
Setting: Neonatal Intensive Care Unit
Intervention: Splint
Comparison: No-splint

Outcomes	*Number of participants (studies) Follow-up*	*Certainty of the evidence (GRADE)*	*Relative effect (95% CI)*	*Anticipated absolute effects*	
				Risk with No-splint	*Risk difference with Splint*
Functional duration of PIVC in neonates	826 (5 RCTs)	⊕⊕◯◯ Low[a,b]	-		MD 3.07 hours lower (5.63 lower to 0.51 lower)
Functional duration of PIVC in term neonates	89 (2 RCTs)	⊕◯◯◯ Very low[a,c,d]	-		MD 3.92 hours higher (4.27 lower to 12.1 higher)
Functional duration of PIVC in preterm neonates	220 (2 RCTs)	⊕⊕◯◯ Low[a,c]	-		MD 5.09 hours lower (9.53 lower to 0.65 lower)
Complications of PIVC	826 (5 RCTs)	⊕◯◯◯ Very low[a,e,f]	RR 1.02 (1.00 to 1.05)	971 per 1,000	19 more per 1,000 (0 fewer to 49 more)

**The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)*
CI: confidence interval; MD: mean difference; RR: risk ratio
[a]Blinding was not done; [b]As the lower CI is 0.5 hours, which is less likely to be clinically significant; [c]Small sample size; [d]CI crosses the line of no difference; [e]High heterogeneity (I^2 is 77%); [f] RR includes 1

complications or at the end of therapy could explain this high complication rate.

Conclusions

Based on the very low to low CoE found in this systematic review, it is not possible to recommend or refute the application of splint to improve the functional duration of PIVC in neonates. Further adequately powered and well-designed studies are needed to assess the effect of splint application in both term and preterm neonates.

Contributors: PS, SrB: Conceptualized the review, literature search, data analysis, and manuscript writing; SaB, MP: Literature search, data analysis, and manuscript writing; JU: literature search, data analysis, and manuscript writing; MP: literature search, data analysis, and manuscript writing; SC: Literature search, and manuscript writing.
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WHAT IS NEW?

- Based on the very low to low certainty of evidence found in this systematic review, it is not possible to recommend or refute splint application in neonates.

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Web Table I Details of Excluded Studies

Study description	*Gupta 2003* [20]	*Tripathi 2008* [21]	*Nema 2018* [22]	*Adhane 2020* [23]
Location	India	India	India	India
Study Design	Cohort	RCT	Quasi-experimental	Prospective
Objective	To survey the use of peripheral IVCs in NICU to ascertain factors influencing their survival	To analyze the various factors that affect the patency of IVCs or are associated with complications	To study the efficacy of splinting the joint on the functional duration of peripheral IVC in neonates	To identify the factors affecting the duration of peripheral IVC in neonates
Inclusion criteria	Admitted newborns needing a peripheral IVC for fluid or drug administration	Children (1 day to 12 years old) consecutively admitted to a pediatric unit and needing IV cannulations	Neonates admitted to NICU	Neonates admitted to NICU
Exclusion criteria	Newborns receiving heparin therapy	Children whose IV was removed prior to discharge	Congenital anomalies, on a ventilator or in the resuscitation process	Not mentioned
Sample size	78 newborns, 166 cannulations	88 children, 377 cannulations	40 neonates	162 neonates
Baseline characteristics	BW ranging from 750-4,100 g (median, 1800 g), GA varying from 28-42 week (median, 36 week)	32% (n = 28) < 30 days; 35% (n = 31) 30 d to 1 y; 22% (n = 19) 1 to 5 y; 11% (n = 10) >5 y	Not mentioned	Mean BW 2080g
Calculated outcomes	Median survival time by Kaplan Meier survival analysis was 40 hours (SE, 2.49, 95% confidence interval 35.12 – 44.88). No significant differences in the IVC life span for various categories of BW (<1,500 (30.7%), 1,500-2,500 (47.3%), >2,500 (22.0%) g), GA (<32 (16.1%), 32-34 (24.2%), >34 (59.7%) w), glucose infusion rate (d”6 (79.5%), >6 (20.5%) mg/kg/min), fluid administration (d”100 (71.1%), >100 (28.9%) mL/kg/d), numbers of attempts at cannulation, site of cannulation, and application of splint.	The use of a splint significantly contributed to cannula patency, mean ± SD of 50.29 ± 20.92 (n=181) with splint vs 39.75 ± 21.39 with no-splint (n=196), P < 0 .005. No effect on the incidence of infiltration with the use of splint but the incidence ofphlebitis was significantly reduced when splints were used.	The mean scores of the splint and no-splint group were 6.35 ± 2.09 and 3.4 ± 1.52, respectively, P = 0.05*	Mean duration of catheter with or without splint was 69.6 h and 61.35 h, respectively, P = 0.08

*BW: Birth weight, GA: Gestational age, IVCs: Intravenous cannulas, NICU: Neonatal Intensive Care Unit, RCT: Randomized controlled trial, SD: Standard deviation,*The basis of scoring was not explained.*

RESEARCH LETTER

Fluid and Parenteral Nutrition Practices in Extreme Preterm Neonates Among Neonatology Practitioners in India: A Web-based Survey

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ABSTRACT

An online survey pertinent to fluid and parenteral nutrition practices in extreme preterm neonates was undertaken with responses from 123 neonatology practitioners across India. The initial fluid rate of 80 mL/kg/day was preferred by 67% neonatologists for 750-1000 g neonates. Half of them increased the fluid rates when weight loss per day was >2%. Practices vary widely across settings and guideline tailor made to clinical conditions is needed.

Keywords: *Guidelines, NICU, Weight loss*

Fluid management and parenteral nutrition (PN) are vital in the management of extremely preterm neonates. Some practice guidelines available for PN in preterm population include NICE Guidelines 2020 [1], Portuguese Neonatal Society 2019 [2] and Australian Consensus Guidelines 2017 [3]. However, the practices vary across the settings according to the available resources and physician's discretion. Hence, this survey was conducted to find the variability in fluid and PN practices in extremely preterm neonates among practitioners across India.

A set of questions related to fluid and PN practices were framed after focused group discussions involving 10 neonatologists with more than ten years-experience in the speciality. Questions pertaining to initial rates of fluid administration on day one of life, subsequent increase in rates of fluid administration, PN practices like providing amino acids, lipids, micronutrients and trace elements in extremely preterm neonates were framed. Ethics clearance was obtained from Institute Ethics Committee. A web-based survey of 25 questions was circulated to neonatologists working in National Neonatology Forum of Delhi (NNF) accredited Level II/III neonatal intensive care units (NICUs) across India. The first part of the survey included a participant information sheet explaining the need and process of the study, and an informed consent form. Once the participants consented, they were directed to the second part of the survey which contained focussed questions.

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A total of 140 neonatologists were approached and 123 responded to the questionnaire. We had representative participation from 33 government hospitals (43%) and 44 private hospitals (57%) from 22 states across India. Majority of participants had 5-10 years of experience (41%) followed by 10-20 years (36%). Extremely preterm babies were uniformly nursed in an incubator by 40% and in a radiant warmer by 38%, while 22% of the respondents used either an incubator or a radiant warmer, according to the availability of incubator.

The responses expressed as *n* (%) are shown in **Table I** and **Table II** depicts the split-up of responses based on the nursing environment. From our survey, we found that initial fluid rates of 80 mL/kg/day as well as 100 mL/kg/day were used equally in neonates born at <26-week gestation. However, the most preferred starting volume for neonates between 26-28 weeks of gestation was 80 mL/kg/day. Parameters considered prior to hiking fluids were: serum sodium (70% of the participants), urine output (64%), weight loss >2%/day (52%) and urine osmolality/specific gravity (4%). The maximum fluid rate hike volume was 20 mL/kg/day (55%) followed by ≥ 30 mL/kg/day in 25%; maximum fluid rate reached was ≤ 150 mL/kg/day (52%), when on PN. When enteral nutrition with fortification was used, maximum TFR (Total fluid rate) was 200 mL/kg/day (45%), followed by 180 mL/kg/day (42%), whereas, when used without fortification, 68% neonatologists preferred to go upto 200 mL/kg/day.

Calcium and phosphorus were added variably beginn-

Table I Responses of the Participants (*n* = 123)

Question	*Response 1* *n (%)*	*Response 2* *n (%)*	*Response 3* *n (%)*	*Response 4* *n (%)*	*Response 5* *n (%)*
Domain I: Fluid Titration					
Initial Starting total fluid volume	80 mL/kg/d	90 mL/kg/d	100 mL/kg/d	110 mL/kg/d	120 mL/kg/d
<26 wk/ <750 g[a]	58 (47)	0	57 (46)	3 (2.5)	3 (2.5)
26-28 wk/750-1000 g[a]	82 (67)	6 (4.8)	33 (26.6)	0	0
Routine hike volume (mL/kg/d)	≤10	15	20	30	Others
<26 wk/<750 g	24 (20)	19 (15)	64 (52)	1 (1)	15 (12)
26-28 wk/750-1000 g	22 (18)	17 (14)	73 (59)	1 (1)	10 (8)
Maximum hike volume (mL/kg/d)	15	20	25	≥ 30	Others
Response	7 (6)	68 (55)	4 (3)	31 (25)	13 (11)
Maximum TFR (mL/kg/d)	≤150	160	180	≥ 200	Others
Parenteral nutrition	64 (52)	24 (20)	21 (17)	10 (8)	4 (3)
Enteral nutrition without fortification	0	12 (10)	27 (22)	84 (68)	0
Enteral nutrition with fortification	0	12 (10)	52 (42)	55 (45)	4 (3)
Frequency of fluid titration	Once a day	Twice a day	At frequent intervals as needed	Once/ Twice as per clinical situation	0
Responses	49 (40)	31 (25)	40 (33)	3 (2)	0
Day of reaching maximum TFR[a]	D 3-4	D 4-5	D 5-6	D 6-7	>7 d
Responses	3 (2.5)	17 (14)	45 (36)	50 (41)	2 (1.5)
Domain 2: Parenteral Nutrition (PN)[a]					
Starting dose in PN (g/kg/d)	1-1.5	2-2.5	3-3.5	4-4.5	Not given
Amino-acids	20 (16)	72 (58.5)	29 (24)	2 (1.5)	-
Lipids	61 (49.5)	34 (27.5)	7 (6)	1 (1)	19 (15.5)
Maximum dose in PN (g/kg/d)	1-1.5	2-2.5	3-3.5	4-4.5	Not given
Amino-acids	0	1 (1)	38 (31)	84 (68)	-
Lipids	1 (0.8)	10 (8)	93 (75.7)	17 (14)	2 (1.5)
Type of lipid used	SMOFlipid	Intralipid	Lipoplus	Omegaven	Not using
Responses	89 (72.4)	19 (15.5)	2 (1.6)	10 (8)	3 (2.5)
When is sodium added to PN	After 24 h	After 48 h	After initial weight loss	After initial diuresis	Based on serum sodium
Responses	3 (2.5)	86 (70)	2 (1.5)	30 (24)	2 (2)
Usual dose in PN (mEq/kg/d)[a]	1	2	3	4	5
Sodium	0	2 (1.5)	83 (67)	27 (22)	9 (7)
Potassium	49 (40)	67 (55)	6 (5)	-	-
Calcium and phosphate in PN	Calcium, phosphate added to TPN	Calcium added, but phos- phorous not added	Calcium and phosphorous not added, when baby is on TPN	Calcium added, but phosphorous given as stat doses at intervals	Others (see text)
Responses	39 (32)	52 (42)	11 (9)	5 (4)	16 (13)
Micronutrients in TPN	Routinely added to TPN	Not added to TPN	Not available	Others	-
Responses	41 (33.5)	65 (53)	3 (2.5)	14 (11)	

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Question	*Response 1 n (%)*	*Response 2 n (%)*	*Response 3 n (%)*	*Response 4 n (%)*	*Response 5 n (%)*
Domain 3: Weight loss					
Weight loss per day (% of birth weight)	<1	1-2	2-3	3-4	Others
Responses	6 (5)	55 (45)	53 (43)	8 (6)	1 (1)
Cumulative weight loss (% of birth weight)	6-10	11-15	15-20	Others	-
Responses	39 (31.5)	77 (62.5)	6 (5)	1 (1)	

PN: Total parenteral nutrition; TFR: Total fluid rate; [a]Missing number are responses other than those mentioned

ing from week 1-3 and, were added depending on the PN duration by 13% of the participants. About half of the participants (53%) did not routinely add trace elements.

Meticulous fluid, electrolyte and nutrition management is an important part of neonatal care. Extremely preterm neonates are the most vulnerable group where fluid titration and PN are vital. There is wide variability with respect to fluid practices among existing guidelines. Australian Consensus Guidelines [3] suggest starting at 60 mL/kg/day, with hiking of 20-30 mL/kg/day. The meta-analysis by Bell et al [4] shows that, neonates receiving restricted fluids showed decrease in necrotizing enterocolitis, patent ductus arteriosus, bronchopulmonary dysplasia and death. Due to the wide clinical heterogeneity in the included trials, direct application of this meta-analysis becomes difficult. Initial fluid rate varies across units and also depends on whether the baby is nursed in a warmer or an incubator [5]. However, titration is often based on clinical parameters, urine output and electrolytes [6].

The meta-analysis by Osborn et al [7] concluded that high amino-acid intake, reduced the risk of post-natal growth failure, increased head growth and decreased the incidence of retinopathy of prematurity (ROP). However, 16% preferred starting amino acids at 1 g/kg. Lipids have a protective role against essential fatty acid deficiency and protein catabolism [8]. However, lipids were not started on day 1 by 16%.

Inadequate supplementation of calcium and phosphorus in the early days of life in these vulnerable population can lead to metabolic bone disease. Though, calcium and phosphorus are recommended from day 1 of PN by all clinical practice guidelines (NICE, Australian and Portuguese), 51% were not adding phosphorus to PN. Around 32% of the participants were adding calcium and phosphorus in PN, whereas, 9% gave calcium in PN via central line and phosphorus through peripheral line. The precipitation while adding both the micronutrients and the potential clinical consequences is the major hindrance in supplementing these in PN [9]. However, this can be avoided by ensuring adequate calcium-phosphorus ratio, amino acid quantity and addition of organic phosphorus.

Zinc supplementation is recommended from day one by NICE Guidelines [1] and Portuguese Guidelines [2]. However, other micronutrients/ trace elements are advised after two weeks of PN by Australian [3] and Portuguese Guidelines [2], whereas, since day one by NICE Guidelines [1]. In our survey, about half of the participants (53%) did not routinely add micronutrients in TPN (Total Parenteral Nutrition). Around 14% prefer to add micronutrients if the neonate required prolonged TPN.

Table II Initial fluid rate based on the nursing environment

Parameter	*Response 1 n (%)*	*Response 2 n (%)*	*Response 3, n (%)*	*Response 4 n (%)*	*Response 5 n (%)*
Incubator (*n*=50)					
Initial starting total fluid volume	≤80 mL/kg/day	90 mL/kg/day	100 mL/kg//day	110 mL/kg/day	≥120 mL/kg/day
< 26 wk/ < 750 g	26 (52)	0	21 (42)	3 (6)	0
26-28 wk/ 750-1000 g	32 (64)	2 (4)	15 (30)	0	0
Radiant Warmer (n=73)					
Initial starting total fluid volume	≤80 mL/kg/day	90 mL/kg/d	100 mL/kg/d	110 mL/kg/d	≥120 mL/kg/d
<26 wk/<750 g	33 (45)	0	36 (49)	0	4 (5.5)
26-28 wk/750-1000 g	51 (70)	4 (5.5)	18 (24.5)	0	0

Classically, a weight loss of 10-15% is accepted in preterm neonates. A postnatal weight loss of <6% is also considered inadequate diuresis by some authors [6]. This is reflected in our study as well, where 63% felt a weight loss of 11-15% is ideal. A daily weight loss of 1-2% was preferred by 45%, followed by 2-3% by 43%.

Thus, there is wide variability in these practices. Consensus was not reached for any question. This underscores the need for formulation of practice guidelines for adaptation across all settings considering the importance of parenteral nutrition, in this vulnerable population.

Ethics clearance: Institutional Ethics Committee, All India Institute of Medical Sciences, Bhubaneswar. Ref Number: T/IM-NF/Neona/22/153

Contributors: AC, UD: Conceptualized the study, developed the study design; AC, TS, PM, Tso, UD: Modified the questionnaire and framed the final version. AC: Reviewed the literature and drafted the initial version of the manuscript; UD, TS, PM, Tso: Reviewed the literature and critically revised the manuscript. All the authors contributed to drafting of the manuscript and approved the final version of the manuscript.

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ERRATUM

Please note the following correction in the Pediatrician's Viewpoint of the Journal Club titled "Short-Course Therapy for Pediatric Urinary Tract Infections" published in Indian Pediatr. 2023;60:765-766. The name of the author of the Pediatrician's Viewpoint should be "Swarnim Swarnim" in place of "Swarnim Ranjan"

Appropriate corrections have already been done in the web version at *https://indianpediatrics.net/sep2023/762.pdf* on December 23, 2023.

ETHISECTION

Ethics of Managing an Adolescent Living with Disability

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ABSTRACT

An ethical challenge arose when the parents of an adolescent girl living with severe intellectual disability requested for a permanent surgical intervention (hysterectomy) that would cause cessation of menstruation and reduce the possibility of pregnancy following nonconsensual sex. The family background was rural with poor access to extended family/community support, financial and social welfare resources. The parental distress was real with the adolescent incompetent to give informed consent. Is a non-therapeutic hysterectomy in an adolescent living with severe intellectual disability ethical? Views of a pediatrician, adolescent specialist, nurse, and an ethicist referring to literature suggesting an approach to an ethical decision are discussed herein.

Keywords: *Ethics, Intellectual Disability, Hysterectomy, Menstruation*

With people living with neuro-disabilities reaching new levels [1], it is not uncommon that general pediatricians need to manage children living with intellectual disabilities in their clinical practice. The challenges which parents, especially mothers, face in providing routine care for such children are immense. The consequences on the primary caretaker's health, family dynamics, social and psychological environments are significant.

CASE DESCRIPTION

A 14-year-old girl with severe intellectual disability (ID) is completely dependent on her mother for all the needs of daily living. The child, though ambulant, is nonverbal, has no hand functions, does not indicate needs and hugs people repeatedly with no obvious stranger anxiety. She shows episodes of aggressive behavior from time to time, worsening during menstruation. The mother traveled from rural Karnataka to an urban tertiary care hospital to solve her problem as suggested by the local physician.

The family is a nuclear family and is facing social challenges while bringing up a child living with a disability. The mother also has new onset hypothyroidism, anemia and is constantly fatigued. The father works full time as a machine operator in a fabrication shop in a nearby town. There is a younger sibling who recently had a seizure and was found to have learning difficulties. This sibling helps the parents take care of the elder sister when the parents are away since the extended family and local community support is poor.

The mother is struggling to deal with the menstrual periods of the child. She is concerned as she is unable to afford or access diapers instead of pads to ensure menstrual hygiene for the child. She is also worried about the child's safety and requests the doctor for a permanent solution like a hysterectomy.

COMMENTARIES

The above child was cared for by a pediatrician (MLL) experienced with caring for children living with disabilities and the case summary was independently shared with an Obstetric Gynecology Specialist Nurse (MRH), an Adolescent Specialist (PMG) and an Ethicist and Physician (GDR) for discussion.

Obstetrics Gynecology Nurse (MRH): The management decisions obviously require a multidisciplinary approach [2]. Management options need to tackle issues that include medical (seizures, behavior); social (security, financial, resources, access to the National Health Mission's (NHM) Menstrual Hygiene Scheme; education (inclusive education); and menstrual hygiene (surgical *vs* non-surgical, therapeutic *vs* nontherapeutic). The guiding principle remains the alignment that the decision has the

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best interests of the child and respects her dignity. Ethical challenges exist where one needs to balance *Autonomy* and *Best Interests*. Does the mother's request for hysterectomy respect the child's well-being, rights and autonomy presuming that there is no medical indication for the surgery? This surgical intervention will lead to sterility of a minor and the consequential improvement in behavior is unclear. Will this decision be considered an ethical allocation of resources? Are the parents truly informed of alternatives and consequences of what she asks for her child?

The most viable solution involves a collaborative effort between health care professionals, social services, and community support to address both medical and socio-economic aspects. Ethical considerations should prioritize the child's best interests while respecting the family's circumstances. Permanent sterilization is not an option of care for this child. Engaging social workers and mobilizing resources to help the child and family may help ease the burden. The availability of other good, long-acting safe contraception methods allows surgical options to be postponed preventing pregnancy, until the behavioral issues settle. A last resort may be that the child be shifted to a facility where she can be supported in all aspects of her care.

Adolescent Pediatrician (PMG): The management should primarily focus on Menstrual Hygiene Management (MHM) and Menstrual Regulation (MR) that is the root cause of the parent's distress. After a detailed history, developmental and nutritional assessment, physical examination, the pediatrician should have a counseling session with both parents in privacy and offer confidentiality. It is vital for the physician to be empathetic, non-judgmental and to validate the mother's concerns. Psychoeducation and education on lifestyle, sexuality, safety, and protection including preventing abuse is imperative. Behavioral challenges may require psychopharmacology through appropriate cross consultations. Accessing regular menstrual pads or diapers through social organizations will help. Unfortunately, presently the NHM Program does not have special provisions for adolescents with disability [3]. MHM and MR options are listed elsewhere [4,5] and may be used during counseling explaining the pros and cons. Major challenges include high costs, adherence to long-term hormonal methods, and long-term consequences of early onset of ovarian dysfunction on bone density and the cardiovascular system including the risk of thrombo-embolism. This would not be complete without providing psychosocial support for the family. If the purpose of the hysterectomy is to stop menstruation, hormonal changes and secure the safety against abuse and pregnancy, then it means an add on oophorectomy though the issue of potential abuse never goes away.

A multi and transdisciplinary team with well-defined management goals would be necessary for management including gynecologists, psychiatrists, psychologists, nursing staff, dietitian, medical social worker, and a medico legal consultant. The goals of management would be formulated in partnership with parents in the best interest of the child after a critical evaluation of all the available options. For example, for menstrual concerns, caregiver education for menstrual hygiene management could be tried and if unsuccessful, hormonal therapy prescribed with close follow up. Unless medically indicated, hysterectomy is not an option for adolescents living with disabilities.

There are many ethical conflicts in this case; the challenges before the family living with resource constraints *vs* the benefit and risks to the adolescent living with severe intellectual disability who is unable to give assent [6]. For an adolescent pediatrician, while deciding a therapeutic option, there is dilemma regarding all the 4 pillars of medical ethics - autonomy, beneficence, non-maleficence, and justice. Decisions regarding the management should be taken in the best interest of the child after obtaining an informed consent from the parents. Hysterectomy has myriad complications and is not indicated for MHM in an adolescent with intellectual disability [7,8], and the parents should be informed regarding the same. Performing hysterectomy in such cases violates reproductive human rights, the right to life and liberty enshrined in the Indian Constitution, the Rights to People with Disability Act 2016 and the Mental Healthcare Act 2017 [9]. Through the medico-legal-ethical lens, psychosocial and medical support to the family along with access to social welfare schemes and education regarding menstrual hygiene and sexuality with regular follow up appears to be the best management strategy in this case.

Ethicist and Physician (GDR): Suppression of menstruation may be temporary by using hormones or it may be permanent by performing a hysterectomy. The advantages of temporary measures are that menstrual bleeding can be reversed, hence preserving the reproductive rights of the person. Disadvantages will be the possible side effects of drugs, recurring costs and need for supervision.

The main ethical challenge remains around reproductive rights of people living with disabilities. *Utilitarianism* or *Teleology* or *Consequentialism* emphasizes that the consequence of the action decides morality and arguably supports the morality of the

hysterectomy. How useful is the action and if it results in the greatest good to the greatest number of persons? Here, the proposed hysterectomy is anticipated to protect the child from pregnancy and helps her hygiene and reduces the work and anxiety of the mother. *Communitarian* ethics focuses on the importance of the community and emphasizes the influence the community has on individuals. This decision will protect the community from unwanted pregnancy, environmental pollution and save time for the mother. The mother has less to worry about the protection and hygiene of the child and can devote more time to the development of both children.

There are ethical theories that do not support this intervention. *Kantianism* or *Deontology* focuses on the process rather than the consequence to decide morality. Decisions based on the physician's duty to always do the right thing. *Reproductive rights* of the child need to be protected. For some, this right trumps over all other rights involved in the case. In the case of *Principlism*, the decision interferes with the autonomy of the child and may have harmful effects. It uses the framework of principles (Respect for Autonomy, Beneficence, Non-maleficence, and Justice) to determine the morality of the action.

OUTCOME

A multidisciplinary cross-consultation approach involving relevant clinical experts, medicolegal and medicosocial workers was used in the situation. Clinical history and examination were reviewed especially regarding development, behavior, function, and competence by cross consultations followed by medico-social assessments. Ideally, hormonal assays and bone age estimation would have been required prior to the onset of menstruation if the same decision was requested proactively. Involving the hospital ethics committee would have allowed for a more informed ethical decision. As pediatricians we remain the child's advocate and hence must be aware of the many downsides involved in agreeing with the parent's request. Ethically, socioeconomic status, inadequate security and birth control measures are not reasons enough for such an intervention. The primary need is to focus on education of the parents and provide support by linking the family to local social welfare networks. No hysterectomy was performed nor advised for the adolescent unless a medical indication arose. The parents, after counseling, agreed to strengthen behavioral management and use linkages to support enabling them to focus on MHM before considering MR while keeping in periodic contact with the Unit of Hope team.

DISCUSSION

The World Health Organization describes Disability as not a disease nor a person, but what arises from an interaction between the person (living with health conditions like cerebral palsy, Down syndrome, etc.) and factors (personal beliefs, fears, goals, preferences, psychological wellbeing, concerns, health literacy, emotional and social factors; and, environmental, socioeconomic, community, cultural and societal expectations). These factors lead to stigma, hence discrimination, which in turn determines disability. ID is defined as "the significantly reduced ability to understand new or complex information and to learn and apply new skills". The onset occurs during the developmental period and includes the presence of significant limitations in intellectual functioning across domains including reasoning, memory, processing speed, and verbal comprehension; and significant limitations in adaptive behavior learned and performed in everyday lives. Severity is determined by considering both the individual's level of intellectual ability and level of adaptive behavior.

Menarche in adolescents living with intellectual disability exposes the varied views of the same by caretakers as well as health care professionals. The role of the environment, especially sociocultural and socio-economic contexts that surround the child living with ID and her family, add to the challenges faced. In our resource-limited settings, psychological distress of caretakers escalates with the emergence of puberty involving reproductive health issues, menstrual hygiene, discomfort, behavioral changes during periods, avoidance of pregnancies, protection against sexual abuse and the inability to care for self.

Ashley was a non-ambulatory 6-year-old girl living with severe, combined developmental and cognitive disabilities and managed by a Seattle Hospital, reported in 2006 [10]. The primary purpose of her management was to enable the continued care of the child at home by parents already faced with daunting tasks, both physical and behavioral. Challenges were as simple as dressing, bathing, diapering, transferring from bed to wheelchair, transporting and dealing with inappropriate unpredictable behaviors. The onset of puberty lead to new fears that pubertal growth spurts would lead to weight gain and the associated menstruation requiring additional care and potential fear of abuse even pregnancy. After much discussion, the hospital went ahead with a hysterectomy, appendectomy, breast-bud removal and administered high dose estrogens to prematurely close epiphysis. This "*Ashley treatment*" remains a focus of much discussion on ethical considerations in dealing with those living with disabilities.

An ethical approach to any challenge needs

consideration of necessity, efficacy, and balancing benefits versus harm [1]. In Ashley's situation, it is argued that the interventions were not necessary for her own wellbeing and even interfered with physiological processes common in all girl children. The indication was not therapeutic since its sole purpose was to enhance the parents' quality of life. Also of concern was that the changes were irreversible and were decided for someone who was incapable of indicating her preferences. Safety of such interventions involving medications, anesthesia and surgery and the paucity of evidence on the effects of high dose hormonal replacement therapy in children fuels the fire. The slippery slope hovers in the background with potential for misuse elsewhere and further demands for invasive procedures since urinary and bowel incontinence also exists. The case presented herein mirrors the parental request similar to Ashley's case.

Surely, this not an easy choice to make, given the existing inequities and resource constraints. Non-therapeutic hysterectomies remain a consideration for people living with disability in low- and middle-income countries. This situation illustrates the need to understand the multiple determinants of health that mandates a multidisciplinary approach while strengthening support systems respecting the rights of people living with disabilities and their caregivers. *Autonomy* requires competence and one presumes that parents remain guardians of their children's best interest. *Beneficence*, i.e., always doing good, keeps the welfare of the child at the center of all decisions. The parent-centered needs, the lack of direct benefit and potential harm to the child exists. *Non-maleficence* and *Primum non nocere* are the pillars of ethics, and here one realizes that the rights of the child to bodily integrity exist. The principle of *Justice* requires all to be treated fairly and equitably. In our situation there are limitations of vulnerability and reliance on the parents. These ethical principles guide us to recognize that there is no role for nontherapeutic hysterectomy for any population, let alone a child living with disability.

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UPDATE

The 2022 International League Against Epilepsy Classification and Definition of Childhood Epilepsy Syndromes: An Update for Pediatricians

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ABSTRACT

The 2017 classification of the epilepsies of International League Against Epilepsy (ILAE) defined three diagnostic levels, including seizure type, epilepsy type and epilepsy syndrome. Epilepsy syndromes have been recognized as distinct electroclinical entities well before the first ILAE classification of Epilepsies and Epilepsy Syndromes in 1985. A formally accepted classification of epilepsy syndromes was not available, and hence, the 2017-2021 Nosology and Definitions Task Force of ILAE was formulated. The ILAE position papers were published in 2022, which classified epilepsy syndromes into (1) syndromes with onset in neonates and infants (up to 2 years of age), (2) syndromes with onset in childhood, (3) syndromes that may begin at a variable age and (4) idiopathic generalized epilepsies. This classification recognized the concept of etiology-specific syndrome. These papers have addressed the specific clinical and laboratory features of epilepsy syndromes and specify the rationale for any significant changes in terminology or definition. This paper will review some pertinent changes and essential points relevant to pediatricians.

Keywords: *Developmental and epileptic encephalopathy, EEG, electroclinical syndromes, Seizures*

The 2017 classification of the epilepsies of International League Against Epilepsy (ILAE) defined three diagnostic levels, including seizure type, epilepsy type and epilepsy syndrome [1]. According to an ILAE report, an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain [2]. In 2014, ILAE defined epilepsy as a disease of the brain characterized by any of the following conditions: *a*) At least two unprovoked (or reflex) seizures occurring > 24 h apart; *b*) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years; *c*) diagnosis of an epilepsy syndrome [3].

Epilepsy syndromes are electroclinical syndromes recognized on the basis of clinical features such as seizure type, age at onset, co-morbid developmental delay, etc., and specific EEG findings. Common examples include West syndrome, Childhood absence epilepsy and Benign Childhood epilepsy with centro-temporal spikes. Epilepsy syndromes have been recognized as distinct electroclinical entities well before the first classification of Epilepsies and Epilepsy Syndromes was proposed by ILAE in 1985 [4]. However, a formally accepted classification and diagnostic criteria of epilepsy syndromes was not available, and hence, the 2017-2021 Nosology and Definitions Task Force of ILAE was assigned this task. This led to the publication of the ILAE 2022 position papers.

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The ILAE position papers are classified into *a*) syndromes with onset in neonates and infants (up to 2 years of age), *b*) syndromes with onset in childhood, *c*) syndromes that may begin at a variable age and *d*) idiopathic generalized epilepsies. For each syndrome, electroclinical criteria, expected results of investigations (imaging, genetics), common co-morbidities, and natural history are provided. This paper will review some relevant changes and important points pertinent to pediatricians.

The Concept of Epilepsy Syndromes

An epilepsy syndromeis defined as "a characteristic cluster of clinical andelectroencephalographic features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious)." The diagnosis of epilepsy syndrome in a child typically has prognostic and treatment implications. These syndromes frequently have age-dependent presentations and a gamut of specific comorbidities.

Epilepsy syndromes are further subdivided into generalized, focal, or generalized and focal, based on the prototype seizure(s), with a separate grouping for syndromes with developmental and epileptic encephalopathy (DEE) or progressive neurological deterioration. The 2017, classification proposed the term DEE to denote epilepsy associated with a developmental impairment that may be due to both the underlying etiology (developmental encephalopathy) and superimposed epileptic activity (epileptic encephalopathy). This approach delineates this group of syndromes associated with cognitive impairment with or without additional manifestations of neurological deterioration. It recognizes that this impairment may be due to the underlying etiology, superimposed epileptic activity, or both.

Moreover, this classification identified the concept of etiology-specific syndrome to define entities with a distinct phenotype associated with a specific etiology; examples include monogenic epilepsies, such as *CDKL5*-DEE, TSC-related epilepsy and *PCDH19* epilepsy, and structural epilepsies, such as mesial temporal lobe epilepsy with hippocampal sclerosis.

These papers have addressed the specific clinical and laboratory features of epilepsy syndromes and provide the rationale for any significant changes in terminology or definition. For each syndrome, three categories of criteria are provided [5].

Mandatory: Criteria that must be present to diagnose the syndrome. If any mandatory criterion is absent, the syndrome cannot be diagnosed.

Alerts: Criteria absent in most cases within a syndrome but rarely can be seen. Alerts alone would not exclude the syndrome but should alert the physician to reappraise the diagnosis and perform further investigations to rule out other conditions. The more alerts present, the less confident one can be about diagnosing a specific syndrome.

Exclusionary: Criteria that must be absent to diagnose the syndrome. If an exclusionary criterion is present, the syndrome cannot be diagnosed.

Other valuable points include how the syndrome may be diagnosed in low-resource settings. For example, some syndromes, e.g. Dravet syndrome, may be diagnosed based on the clinical features alone, and EEG, MRI and genetic testing are not essential for diagnosis in a low-resource setting. The other significant change is that the terminology of "benign" has been replaced by "self-limited", recognizing that these formerly "benign" termed syndromes do have intellectual and behavioral co-morbidities. For example, benign childhood epilepsy with centro-temporal spikes (BECTS) has been renamed Self Limited Childhood Epilepsy with Centro-temporal spikes (SeLECTS). Lastly, most named syndromes have been replaced with descriptive nomenclature. For example, West syndrome is now called "Infantile Epileptic Spasms Syndrome". However, there are some exceptions where the eponyms have been preserved, e.g. Lennox Gastaut syndrome and Dravet syndrome.

It is beyond the scope of this article to discuss the criteria for the individual syndromes. This review will be restricted to the nomenclature and classification. The reader is encouraged to refer to the original ILAE papers for the criteria required for syndromic diagnosis of various epilepsy syndromes. For a basic understanding of seizure and epilepsy classification in children and its modification in neonates, the reader is referred to the relevant papers [1,6]. A list of electroclinical syndromes with their previous and current terminology according to recent ILAE classification has been provided in **Table I**.

Epilepsy with Onset in the Neonatal Period and Infancy

This subset has been divided into two major groups: self-limited epilepsy syndromes, where spontaneous remission is the rule, and the DEEs, where there is developmental/cognitive impairment related to both the underlying etiology independent of epileptiform activity and the epileptic encephalopathy. Most etiology-specific syndromes that have onset in the neonatal or infantile period are DEEs [7].

The term "benign" has been replaced with self-limited as explained earlier. The common entity "Benign familial neonatal convulsions" has been replaced with "self-limited neonatal epilepsy."

As explained earlier, transparent terms that describe the clinical condition, such as Infantile epileptic spasms syndrome (IESS), have been proposed instead of the eponymous West syndrome. The aim is toenable early diagnosis and appropriate treatment. Many infants do not fulfill the triad of West syndrome, as they may lack hypsarrhythmia or regression hence, the term IESS is proposed.

Previous classifications for infantile-onset epileptic encephalopathy included two syndromes: Ohtahara syndrome and Early Myoclonic Encephalopathy. There is an electroclinical overlap between these two, sharing genetic and structural etiologies. Furthermore, many infants do not meet the criteria for either syndrome, highlighting the broad spectrum of presentations within Early-infantile developmental and epileptic encephalopathy (EIDEE). Thus, the Task Force amalgamated these into one syndrome called EIDEE. Syndromes that

Table I List of Electroclinical Syndromes With Their Previous and Current Terminology According to Recent ILAE Classification

	Current terminology	*Previous term*
Self-limited epilepsies	Self- limited (familial) neonatal epilepsy (SeLNE) Self- limited familial neonatal- infantile epilepsy (SeLFNIE) Self-limited infantile epilepsyGenetic epilepsy with febrile seizures plus (GEFS+) spectrum Myoclonic epilepsy in infancy (MEI)	Bening familial neonatal convulsions Bening familial neonatal/infantile seizures
Developmental epileptic encephalopathies (DEE)	Early infantile developmental epileptic encephalopathy Epilepsy in infancy with migrating focal seizures Infantile epilepsy spasms syndrome Dravet syndrome	Ohtahara syndrome and Early myoclonic encephalopathy of infancy Migrating partial seizures of infancy West syndrome Severe myoclonic epilepsy of infancy
Etiology specific syndrome	KCNQ2- DEE Pyridoxine-dependent (ALDH7A1)- DEE (PD- DEE) and pyridox (AM) INE 5'-phosphate deficiency (PNPO)- DEE (P5PD- DEE) CDKL5- DEE PCDH19 clustering epilepsy GLUT1DS Sturge–Weber syndrome	
Self- limited focal epilepsies Epilepsy syndromes with focal seizures	Self- limited epilepsy with centrotemporal spikes (SeLECTS)	Childhood epilepsy with centrotemporal spikes, (benign) Rolandic epilepsy, (benign) epilepsy with centrotemporal spikes
	Self- limited epilepsy with autonomic seizures (SeLEAS)	Panayiotopoulos syndrome, early onset (benign) occipital epilepsy
	Childhood occipital visual epilepsy (COVE)	Late onset (benign) occipital epilepsy or idiopathic childhood occipital epilepsy–Gastaut type
	Photosensitive occipital lobe epilepsy (POLE)	Idiopathic photosensitive occipital lobe epilepsy
Genetic generalized epilepsies	Childhood absence epilepsy (CAE)	Pyknolepsy, petit mal
Epilepsy syndromes with generalized seizures	Epilepsy with eyelid myoclonia (EEM)	Jeavons syndrome
DEEs	Epilepsy with myoclonic absence (EMA)	Bureau and Tassinari syndrome
	Epilepsy with myoclonic atonic seizures Lennox–Gastaut syndrome DEE-SWAS and EE-SWAS Febrile infection- related epilepsy syndrome (FIRES) Hemiconvulsion–hemiplegia–epilepsy syndrome (HHE)	Doose syndrome.

contained terms such as severe (severe myoclonic epilepsy in infancy), malignant (malignant migrating partial seizures in infancy), and benign (benign neonatal seizures) were changed to align with the most recent update.

Similarly, the term "partial seizures" has been replaced by "focal-onset seizures." To avoid confusion between seizure types and epilepsy syndrome, the term "convulsions" was replaced with "epilepsies" in some syndromes such as Self-Limited Neonatal Epilepsy. Moreover, because only family history differentiates between Familial and Non- familial Self-limited neonatal and infantile epilepsies, they merged these using the terms "Self-limited (Familial) Neonatal Epilepsy" and "Self-limited (Familial) Infantile Epilepsy," which allows the term "familial" to be used wherever appropriate. Finally, the concept of etiology-specific syndromes for certain

genetic and structural etiologies have been introduced. Gene discoveries have allowed the delineation of new electro-clinical syndromes, such as KCNQ2-DEE and CDKL5- DEE. Etiology-specific syndromes would mean rapid diagnosis and optimization of anti-seizure medications for the specific syndrome if available (e.g. sodium channel blockers for KCNQ2-DEE), and they allow the possibility for precision medicine trials/therapies, which will improve long-term prognosis.

Epilepsy Syndromes with Onset in Childhood

Epilepsy syndromes of childhood onset (age 2-12 years) have been divided into three categories: *a*) self-limited focal epilepsies (SeLFE), comprising four syndromes: self-limited epilepsy with centrotemporal spikes, self-limited epilepsy with autonomic seizures, childhood occipital visual epilepsy, and photosensitive occipital lobe epilepsy; *b*) generalized epilepsies, comprising three syndromes: childhood absence epilepsy, epilepsy with myoclonic absence, and epilepsy with eyelid myoclonia; and *c*) developmental and/or epileptic encephalopathies (DEEs), comprising five syndromes: epilepsy with myoclonic–atonic seizures, Lennox–Gastaut syndrome, developmental and/or epileptic encephalopathy with spike and wave activation in sleep, hemiconvulsion–hemiplegia–epilepsy syndrome (HHES), and febrile infection-related epilepsy syndrome (FIRES) [8].

Recognition of these childhood syndromes requires knowledge of seizure semiology, temporal evolution, and the developmental status of the child, as well as electroencephalographic (EEG) features (background, interictal, and ictal patterns) and, in some cases, brain magnetic resonance imaging (MRI) and genetic studies. The name "SeLFE" was chosen to reflect the key features of the natural history and the clinical phenotype. The term "benign" is inappropriate, as some children have associated cognitive and behavioral comorbidities. For each syndrome, the terms used reflect the major phenotypic features, such as centrotemporal spikes in SeLECTs, autonomic seizures in SeLEAS, occipital semiology and EEG findings in childhood occipital visual epilepsy (COVE), and photic-induced focal sensory visual seizures and genetic predisposition in photosensitive occipital epilepsy (POLE).

Regarding the childhood-onset DEEs, not uncommonly, childhood syndromes may have evolved from pre-existing epilepsy syndromes, such as infantile epileptic spasms syndrome, which typically evolve to LGS in up to one-third of patients, or self-limited epilepsy with centrotemporal spikes (SeLECTS; formerly known as benign rolandic epilepsy or benign epilepsy with centrotemporal spikes) or structural focal epilepsy evolving to epileptic encephalopathy with spike-wave activation in sleep (EE-SWAS). In acquired syndromes, they are typically developing children present with a profound acute encephalopathy followed by drug-resistant epilepsy, as seen in FIRES, or HHE. Moreover, some self-limited focal epilepsies may overlap with the idiopathic generalized epilepsies (IGEs) or even evolution to IGEs.

Developmental/Epileptic Encephalopathy with Spike Wave Activation on Sleep (DEE-SWAS) (DEE-SWAS) and Epileptic Encephalopathy with Spike Wave Activation on Sleep (EE-SWAS) refer to a spectrum of conditions that are characterized by various combinations of cognitive, language, behavioral, and motor regression associated with striking spike and wave activation in NREM sleep. DEE- SWAS and EE- SWAS share similar clinical features. These were previously called by various terms such as Landau Kleffner Syndrome, Electrical Status Epilepticus in Sleep, and epileptic encephalopathy–continuous spike and waves during sleep. Similarly, the terms DEE-SWAS and EE-SWAS comprise two essential components, cognitive regression and the characteristic EEG pattern.

Epilepsy Syndromes with Onsset at a Variable Age

Although many epilepsy syndromes typically begin in the neonatal period, infancy, or childhood, several important syndromes begin at a variable age, which have treatment implications if recognized appropriately [9].

Syndromes that begin at a variable age can begin in those aged ≤ 18 years and in those aged ≥ 19 years. These syndromes can be broadly classified into generalized, focal, and combined generalized and focal epilepsy syndromes. Some syndromes can be associated with developmental and/or epileptic encephalopathy in children or with progressive neurological deterioration if they begin later in life.

Generalized epilepsy syndromes with polygenic etiologies, include idiopathic generalized epilepsies (IGEs), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures alone (GTCA).

Focal epilepsy syndromes include self-limited focal epilepsy syndromes with presumed complex inheritance: childhood occipital visual epilepsy (COVE) and photosensitive occipital lobe epilepsy (POLE).

Focal epilepsy syndromes with genetic, structural, or genetic–structural etiologies: sleep-related hypermotor (hyperkinetic) epilepsy (SHE), familial mesial temporal lobe epilepsy (FMTLE), familial focal epilepsy with

variable foci (FFEVF), and epilepsy with auditory features (EAF)

A combined generalized and focal epilepsy syndrome with polygenic etiology: epilepsy with reading-induced seizures (EwRIS)

Epilepsy syndromes with developmental encephalo-pathy (DE), epileptic encephalopathy (EE), or both, and epilepsy syndromes with progressive neurological deterioration: progressive myoclonus epilepsies (PME) and febrile infection-related epilepsy syndrome (FIRES).

Two other etiology-specific epilepsy syndromes have seizure onset at variable ages, which are of importance under this category:

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE- HS)
- Rasmussen syndrome (RS)

Idiopathic Generalized Epilepsy Syndromes

The term idiopathic generalized epilepsies (IGEs) had historically included the syndromes childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic–clonic seizures alone (GTCA). The 2017 ILAE classification suggested that the term "genetic generalized epilepsies" (GGEs) be used for the broad group of epilepsies with generalized seizure types and generalized EEG abnormalities based on a presumed genetic etiology. The task force proposed that the term IGE should pertain to a distinct subgroup of the GGEs comprising of these four syndromes for the following reasons: They are the most common GGE syndromes. They typically have a good prognosis for seizure control. They typically do not evolve to epileptic encephalopathy. There is clinical overlap between CAE, JAE, and JME. They may evolve with age to another IGE syndrome (e.g., CAE evolving to JME). They have similar electroencephalographic (EEG) findings, including a normal background activity with 2.5-6 Hz generalized spike-wave and/or polyspike-wave discharges that may activate on hyperventilation and photic stimulation [10].

These current definitions and classifications of epilepsy syndromes by ILAE will enable clinicians to early characterize epilepsy syndromes, offer appropriate treatments and prognostication. With contributions from genetic research, the phenotypic spectrum for epilepsy syndromes has expanded and etiology-specific epilepsy syndromes are increasingly recognized. There is a word of caution about the strict delineation of epilepsy syndromes, which can be potentially harmful if they exclude patients who do not precisely meet the criteria. Future work establishing diagnostic criteria for etiology-specific epilepsy syndromes will be necessary for research into precision therapies [e.g., Mammalian target of rapamycin (mTOR) inhibitors for tuberous sclerosis], advancing knowledge of pathogenesis and identifying subgroups within specific etiologies with a better treatment response. Future ILAE classifications may throw more light on this perspective.

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Strolling Through Half a Century of Adolescent Growth

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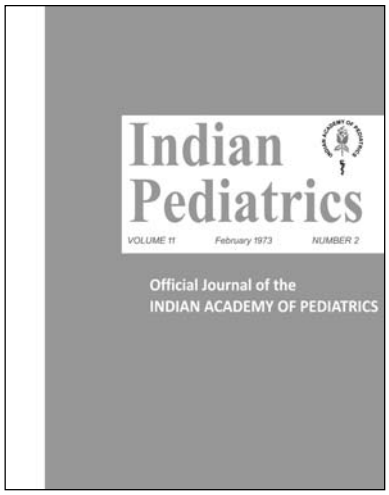
Growth of children has changed dramatically over the last century. India has faced severe starvation of its population during the heartbreaking famine in 1943 [1]. Since independence, the country has moved forward gradually to provide enough nutrition to a significant proportion of its citizens. With economic progress over the next three decades, there was a gradual improvement in nutrition of children. But, some of them continued to remain deficient [2]. Very few children were obese then.



Adolescence is a period of transition from a child to an adult with growth being an integral part of this change. Along with this, the development of psychological and adaptive behavioral changes bring about extensive transformation. Any adversity during this period spanning almost a decade could have an enormous impact on the health of the person and the society.

From an era of deficiency to near normalcy to a period of abundant nutrition, there has been a huge shift in the nutritional status of adolescents since then. The changes in the pattern of growth of adolescent children over the last 50 years is examined in this article.

THE PAST

A pioneering research by Agarwal *et al* in in February 1973 in *Indian Pediatrics* assessed the physical growth in 3555 healthy adolescents in Varanasi and characterized their anthropometric measurements including height, weight, chest circumference, skull circumference, mid-arm circumference and mid-leg circumference [3].

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Evaluation of growth during adolescence extended from 9-17 years in boys and from 8-17 years in girls. Weight gain among boys was similar across all socio-economic groups. But, the weight gain among girls was earlier in socio-economic group 1 and a year later in the other groups; the quantum of weight gain being slightly different among different groups.

Height gain was 36 cm over 7 years in boys belonging to socio-economic group 1 and 32 cm over 8 years in boys from socio-economic groups 2 and 3. Height gain among girls was maximum between 8-12 years in group 1 and between 8-13 years in group 2 and 8-14 years in group 3. The authors had noted that the girls were heavier and taller than boys at the ages of 9-13 years, while the boys outgrew the girls a bit later.

Chest circumference gain was the same across all groups of girls, albeit at different ages. Boys had a similar gain in chest circumference among groups with the maximum gain happening between 12-15 years.

The mid-arm circumference was similar at 9 years of age in either sex and was the same across both sexes at completion of growth. An identical picture was evident in the mid-leg circumference in both sexes at 9 years of age and at completion of adolescence, across all socio-economic groups.

THE PRESENT

A huge disparity exists between the final heights achieved by boys and girls at the completion of growth among the population from rural areas of different states in India. The National Nutrition Monitoring Bureau has noted an increase of 3.1 cm in boys and 1 cm in girls over a period of 35 years from the 1970s to 2012-2013 [4]. The Southern states of Tamil Nadu and Kerala are reflecting a secular trend with the final height potential matching that of Europeans. The boys from Kerala at the age of 18+ years

show a secular trend in final height with a gain of 7.4 cm and the girls reveal a gain of 4.8 cm over 35 years. Boys from Tamil Nadu over 35 years have revealed a secular trend in height with an additional 7.3 cm among boys and 3.8 cm among girls.

The height of boys at 13 years was 149-150.7 cm and weight was 37 kg, while the girls were 146.88-150.29 cm tall and weighed 36-40 kg in 1973. But, 13.5-year-old boys measured 154.5 cm and girls 152.9 cm in stature with a weight 40.7 kg among boys and 42.7 among girls of rural Mysore in 2015. In contrast, the weight of boys and girls of rural India in 2015 at 9 years of age in the pre-pubertal stage is almost similar to urban boys and girls of 1973.

Thus, there has been a secular trend of increased weight and height among adolescents over the last 50 years. Over the last half century, gain in weight has been more significant than height among the adolescents. This is reflected in the prevalence of obesity among adolescents with 5.3% of males and 5.2% of girls under 20 years of age being overweight and 2.3% and 2.5% of boys and girls in this age group being obese in 2013 [5]. A later study published in *Indian Pediatrics* in February 2023 revealed a prevalence of 15% overweight status and 5% obesity in a cohort of boys aged 6-15 years in Bengaluru, India [6]. The authors noted that the walkability index of the local area was negatively associated with obesity and body fat. A study in 2019 from Karnataka has noted the incidence of overweight/obesity in adolescence to be a staggering 17% [7] while a study noted obesity related hypertension in adolescents of Punjab [8]. Several studies have noted the higher risk for obesity with increased consumption of highly processed high calorie foods, higher exposure to media and reduced physical activity. The risk of overweight/obesity even in the under-five children is an alarming 2.6% [9].

THE FUTURE

Our country is in a period of transition in terms of physical growth of its children and socio-economic status of the families. This has led to secular change in growth of our children that matches the well-nourished Europeans [10]. With an increase in the availability of cheap, well-packaged processed foods across all sections of our population, our younger sections of society are facing an unprecedented rise in obesity. This puts them at a higher risk of metabolic disorders including type 2 diabetes mellitus, systemic hypertension, cardiovascular diseases, musculoskeletal disorders and cancers [11]. 30-60% of adult health disorders are due to events that happened during adolescence. Our focus in future would be to raise awareness of non-communicable diseases among our families to improve the health of our youngsters and preserve them to face a healthy future.

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Expansion of Phenotypic Spectrum in Hyperphosphatemic Familial Tumoral Calcinosis

Hyperphosphatemic familial tumoral calcinosis (HFTC) is a rare genetic condition caused due to disease-causing variants in genes *FGF23* (MIM*605380), *GALNT3* (MIM*601756) and the *FGF23* co-receptor encoded by *áKlotho* (á*KL*) (MIM*604824). Fibroblast growth factor 23 (*FGF23*) is a peptide hormone which acts as a chief regulator of serum phosphorous levels in the body. *FGF23* is post-translationally processed in the golgi apparatus via O-glycosylation by the *GALNT3* gene [1]. Variants in *FGF23* and *GALNT3* genes result in deceased *FGF23* levels. Variants in *αKL* causes resistance to *FGF23* activity. Hence, deficiency of *FGF23* or resistance to it results in increased renal phosphate reabsorption, consequently hyperphosphatemia and elevated or normal 1,25 dihydroxy vitamin D (1,25D) production is seen. Increased levels of 1,25D in turn promote gastrointestinal absorption of phosphorus and calcium. Elevated blood calcium-phosphorous product predisposes to ectopic calcification mostly in soft tissues exposed to repetitive trauma, prolonged pressure or inflammation [2].

Till date, fewer than 100 families with a definitive molecular diagnosis of HFTC have been reported in literature [1]. We hereby report three individuals from three unrelated Indian families with disease causing variants of *FGF23* and *GALNT3*. Targeted gene sequencing of *GALNT3* and *FGF23* was performed by amplifying all coding exons of *GALNT3* and *FGF23* using PCR and bidirectional sequencing for proband 1 and 2. Singleton exome sequencing (Illumina, Inc. San Diego, CA) was performed for proband 3 as described previously [3]. The exome sequencing data was processed using ANNOVAR and customised scripts [4]. Validation and segregation analysis of the identified variant was performed by Sanger sequencing for proband 1 and 3.

Proband 1: A 5-year-6-month-old girl, second-born to non-consanguineously married parents, presented with swelling on right elbow of one-year-duration. On examination, her height was 115 cm and her weight was 18.7 kg. Radiograph of the right elbow showed soft tissue calcification (**Fig. 1A** and **1B**). Blood investigations showed elevated phosphorous and low levels of parathyroid hormone. She had increased tubular reabsorption of phosphate (TRP) suggested by the ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR) which was disproportionate to her hyperphosphatemia. Following excision of the tumor, the child was lost to follow up.

Proband 2: A 22-year-old lady, first-born child to a third-degree consanguineously married parents presented with complaints of pain in soles, knees and hips. She had a restriction in movement near the joints for the past two years. Her previous records showed documentation of hyperphosphatemia on two occasions. On examination, she had a large forehead and signs of poor dental health. Her height was 154 cm (Z score -1.43) and weight was 33 kg (Z score -3.65). Radiographic imaging showed calcification in the 7th, 8th and 9th ribs (**Fig. 1C**). She had hyperphosphatemia, low normal parathyroid hormone levels, elevated TRP and TmP/GFR.

Proband 3: A 13-year-old boy, fourth-born to a second degree consanguineously married parents, presented with complaints of pain in hip, limping gait and difficulty in squatting for one month. Past history revealed two episodes of Bell's palsy, at 4 years and 6 years of age, respectively. On examination, he had relative macrocephaly, left eye esotropia, myopia, bilateral pterygia and pectus carinatum. There were no ossified lesions. Cranial nerve examination showed left sided facial palsy. His height was 143 cm (Z score -1.68), his weight was 24.2 kg (Z score -3.18) and head circumference was 55 cm (Z score +0.54). He had hyperphosphatemia, normal parathyroid levels, vitamin D deficiency (25-OH vitamin D level: 8.83 ng/mL), and an elevated TRP and Tmp/GFR, C-terminal FGF23 and 1,25–vitamin D levels. Radiographs were suggestive of patchy osteosclerosis and osteopenia, calcification in the diaphysis of the femur, sandwich vertebrae, bilateral valgus slipped capital femoral epiphysis (SCFE) and hyperostosis of metacarpals (**Fig. 1D, 1E** and **1F**). The orthopantomogram showed obliteration of the dental pulp and thistle-shaped root (**Fig. 1G**). Arterial doppler of upper and lower limbs showed diffuse vascular calcification in both the upper and lower limb arteries. The child underwent bilateral in situ pinning and lateral hemi-epiphysiodesis of distal femur and proximal tibia for SCFE. On follow-up after a year, he had persistent hypercalcemia and hyperphosphatemia. There were no new lesions or signs of vascular insufficiency.

A known missense variant, NM_004482.3:c.1097T>G p.(Leu366Arg) and a known stop gain variant

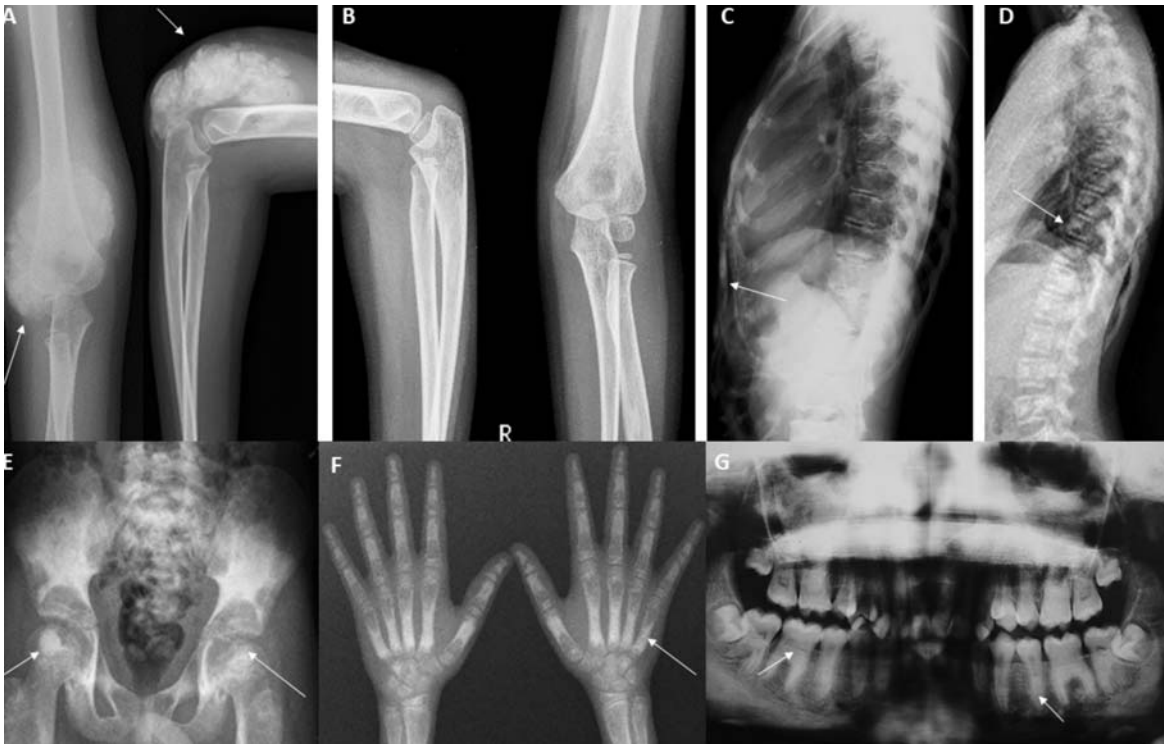

Fig. 1 A. Calcified mass near soft tissues in proband 1. **B.** Post-operative radiograph of proband 1 after excision of calcified mass. **C.** Calcification in the 7th, 8th and 9th ribs in proband 2. **D.** Sandwich vertebrae in proband 3. **E.** Calcification in the diaphysis of the femur, bilateral valgus slipped capital femoral epiphysis, patchy osteosclerosis and osteopenia in proband 3. **F.** Calcification or hyperostosis of metacarpals in proband 3. **G.** Orthopantomogram of proband 3 showing obliteration of the dental pulp and thistle-shaped root (depicted by arrows)

NM_004482.3:c.1576G>T p.(Gly526Ter) in *GALNT3* was identified in proband 1 in compound heterozygous state. Her parents were heterozygous carriers for the stop gain and non-synonymous variant respectively. On classification according ACMG criteria, the missense variant is likely pathogenic, and the stop gain variant is pathogenic [5].

A known missense variant, NM_020638.2:c.385T>C p.(Ser129Pro) in *FGF23* was identified in proband 2 and 3. Validation and segregation of the variant was performed for proband 3 and both his parents were heterozygous carriers. On ACMG classification, it is likely pathogenic [6].

Table I depicts the clinical, laboratory and genetic profile of all three cases. Herein, we report three individuals with HFTC caused due to biallelic loss of function variants in *GALNT3* and *FGF23*. All three individuals had elevated levels of serum phosphorous levels and normal levels of calcium. Decreased levels of parathyroid hormone were observed in proband 1. Proband 2 and 3 had parathyroid hormone levels at the lower end of the normal range. Proband 1 had a huge lesion requiring surgical excision. Cranial nerve examination of proband 3 showed left sided facial palsy that has been previously described in one individual with HFTC [7]. Hyperphosphatemia, increased TRP, TmP/GFR and ectopic calcification were consistently seen in all three probands. It is worthwhile to notice asymptomatic, although severe vascular calcification was observed in proband 3. In such individuals, it is prudent to follow up closely for signs of vascular insufficiency and to intervene early, if needed. In addition, proband 3 also had bilateral valgus SCFE. To our knowledge, this phenotype has not been reported in HFTC and adds to the phenotypic spectrum of the condition.

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Table I Genetic Variant Details and Blood Investigations of Proband and 1, 2 and 3

Parameter	*Proband 1*	*Proband 2*	*Proband 3*
Urea (mg/dL)	21	20	14
Creatinine (mg/dL)	0.4	0.4	0.44
Sodium (mg/dL)	134	138	142
Potassium (mg/dL)	4.8	4.5	5.1
Calcium (mg/dL)	10.0	9.3	10.7
Phosphorous (mg/dL)	8.7	6.9	8.7
Serum alkaline phosphatise (IU/L)	136	50	178
25OH-vitamin D (ng/mL)	18.27	—	8.83
Parathyroid hormone (pg/mL)	12.18	18.71	16.9
TRP (<0.9)	0.97	0.90	0.96
TmP/GFR (<5 mg/dL)	> 5	>5	>5
FGF23 (0 – 150 RU/mL)	-	-	6670
1,25-dihydroxy-vitamin D (pg/mL)	-	-	304
Molecular analysis			
Gene	*GALNT3*	*FGF23*	*FGF23*
Transcript ID	NM_004482.3	NM_020638.2	NM_020638.2
Variant	c.[1097T>C]; [1576G>T] p.[(Leu366Arg)]; [(Gly526*)]	c.385T>Cp. (Ser129Pro)	c.385T>Cp. (Ser129Pro)
Zygosity	Compound heterozygous	Homozygous	Homozygous
ACMG classification	Likely pathogenic; Pathogenic	Likely pathogenic	Likely pathogenic

ACMG: American College of Medical Genetics and Genomics; FGF23: Fibroblast growth factor 23; TmP: Tubular maximum reabsorption of phosphate; GFR: Glomerular filtration rate; TRP: Transient receptor potential

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Indian Academy of Pediatrics (IAP) Immunization and Developmental Card - an Easy way for Developmental Monitoring and Early Identification of Neurodevelopmental Problems

Early identification of neurodevelopmental disorders (NDDs) by a single tool as well as monitoring of children with NDDs is essential [1]. Simplified methods and tools are required for this [2]. A novel "Development Assessment Chart Incorporated Immunization Card" was designed by combining the immunization and salient developmental milestones on the same page. Developmental milestones in all the domains [3] were suitably combined with the IAP Immunization Schedule [4] in one card [5], with suitable pictures along with early markers of autism spectrum disorder (ASD) and learning disorders (LDs). After scrutiny and approval by the state chapter of Indian Academy of Pediatrics (IAP) in November 2020, the card was released in an online meeting organized on the Digital Indian Academy of Pediatrics (dIAP) platform. Approvals from the Advisory Committee on Vaccines and Immunization Practices (ACVIP) and the Neurodevelopmental Chapter of IAP were received in January 2022. The card so developed was also translated in Tamil language.

This card was field tested in the Cuddalore district of Tamil Nadu. During the frequent immunization visits in the first year and periodically thereafter, developmental monitoring, alongside vaccination, was considered a possible working model. To educate the parents, a 20-page booklet on "Upgraded parenting and child developmental guide" [6] along with the card was distributed in Cuddalore District by the pediatricians during the immunization visits, to all the postnatal mothers, with the permission of the Directorate of Public Health, and with financial support from Neyveli Lignite Corporation (NLC), a public sector undertaking of the Government of India. Nearly 1,00,000 booklets were distributed. A QR code was placed on the back page of the booklet using which the parents could access the YouTube link to enable them to listen to in Tamil language to the importance of developmental monitoring, methods to use the card to ascertain developmental delay and what they needed to do if they identified a developmental delay. The card and the booklet were sent by mail to all the members of the IAP from the IAP central office in December 2022.

The acceptability and utility of the card were very good, as evidenced by the electronic feedback received. These cards were sent to all the members of the IAP in Cuddalore district, and feedback was obtained from 103 pediatricians. More than 90% found that the card was useful and encountered no difficulty in using it. Five parents of children with developmental delays approached the author directly after using the card and the booklet without being referred by any doctor, out of whom four were diagnosed with autism spectrum disorder (ASD). More than 100 children with NDD were identified by pediatricians in the Cuddalore District in the 12-month period (January 2022–December 2022).

This novel card may prove to be a vital link in routine developmental assessment by any health care worker involved in immunization. Research on the utility of the card for early recognition of undiagnosed NDDs should be tested in various settings.

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Effect of Oral Zinc in Management of Hyperbilirubinemia in Term Neonates

We read with interest the article on effects of zinc supplementation on serum bilirubin levels in term neonates with hyperbilirubinemia undergoing phototherapy [1]. We would like to highlight and seek clarifications regarding certain aspects of the study.

Dehydration is a common cause of neonatal hyperbilirubinemia and can be a cause of increased enterohepatic circulation leading to hyperbilirubinemia. The weight of the babies at the time of enrolment has not been mentioned. It has been mentioned in the study that all babies who were enrolled were given breast milk and spoon feeds. It is logical to assume that after enrolment, feeding in the neonatal intensive care unit (NICU) would have been regularized and all babies would now be getting adequate milk orally. This in turn will reduce the enterohepatic circulation, leading to faster reduction in bilirubin levels of the babies. Hence, NICU admission weight, comparison of percentage of weight loss and to some extent stool output between zinc group and placebo group would have provided additional information and removal of bias due to regularization of feeds.

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AUTHORS' REPLY

We appreciate the interest in our article [1] and the insightful comments from the readers. We agree with the author's comment that dehydration can exacerbate hyperbilirubinemia by increasing enterohepatic circulation. In our study, all neonates were closely monitored, and none had clinical signs of dehydration.

The inclusion criteria in our study ensured all infants were term neonates and that birth weights were comparable between the groups. We agree that regular feeding practices in the NICU could potentially impact bilirubin levels. However, all infants received standardized feeding protocols regardless of group allocation, and we maintained a randomized controlled trial design and double-blinding to minimize the potential bias due to feeding practices. Additionally, the significant difference in bilirubin reduction observed between the groups strongly suggests an effect of zinc supplementation.

We acknowledge that comparing weight loss and stool output between the zinc and placebo groups could have provided valuable data. We recommend including such analysis in future studies.

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Critical Considerations on Interpreting N-Terminal Pro-Brain Natriuretic Peptide levels in Kawasaki Disease

We read with interest the study by Banerjee et al on N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) levels in Kawasaki Disease (KD) [1]. The authors reported that the number of KD patients whose NT-proBNP was elevated (n = 28) were significantly higher compared to controls (70% vs 32.5%; $P < 0.001$). Also, children with incomplete presentations of KD had higher NT-proBNP levels than controls (84% vs 4%; $P < 0.001$). It is appropriately mentioned that difficulty in identifying incomplete and atypical presentations of KD could delay the diagnosis and increase the risk of coronary involvement [2]. Therefore, in this study, it would be interesting to know the proportion ofz incomplete KD among the cases and the number of incomplete KD cases that had higher NT-proBNP levels. The apparently high proportion of incomplete KD patients with elevated NT-proBNP (84%) compared to complete KD (70%) and controls (4%) in this study indicates that elevated NT-proBNP levels may have played a role in the diagnosis of incomplete KD. This could have potentially introduced a selection bias.

In current clinical practice, it is compelling to use age-specific centiles for NT-proBNP in contrast to a fixed cut off value (225 pg/mL) as considered in the study [3,4]. NT-proBNP levels are known to decrease with age, from 400 pg/mL at 3 months to 138 pg/mL (female) and 65 pg/mL (males) by puberty, and even within the 1-2 years age-group, the cut offs vary between 316 to 675 pg/mL [4]. Using a single value instead of age- and gender-stratified cut-offs could be potentially misleading.

Interpreting NT-proBNP thresholds also requires careful consideration of the specific patient population and clinical context in which the test is being used. A recent meta-analysis of pooled data from 12 studies (2173 cases and 1909 controls) indicated that NT-proBNP has a moderate diagnostic accuracy for KD with the pooled sensitivity and specificity of 0.80 (95% CI: 0.72-0.86) and 0.81 (95% CI: 0.73-0.88), respectively [5]. Prevalence-adjusted NT-proBNP thresholds potentially improve the test's performance. In areas where KD is not widespread (prevalence < 10%), a negative NT-proBNP test provides strong evidence against KD [5].

The clinicians need to consider the individual patient's risk factors and clinical judgement in addition to prevalence of KD in their setting when assessing the likelihood of KD while interpreting NT-proBNP values. Especially in cases of incomplete presentations of KD; understanding the patient's pre-test probability can be crucial for accurate diagnosis. For practitioners in low-prevalence settings, dependence on NT-proBNP as a diagnostic tool may lead to over diagnosis and unnecessary interventions.

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AUTHORS' REPLY

We thank the authors for carefully reading our article on NT-proBNP levels in Kawasaki Disease (KD) and the accompanying critical appraisal. Their query is mainly centered around "It was also shown that even patients with incomplete KD had higher NT-proBNP levels than febrile control group (84% vs 4%; $P < 0.001$)." However, this was not mentioned in the results of our study and was mentioned in the paragraph in the discussion section where we discussed our study findings in comparison to previous published articles. This particular finding was from the study published by Rodriguez-Gonzalez et al in Emergencias in 2019 [1]. We faultily missed out adding the reference. Thus, the presumption that elevated levels in incomplete KD patients resulted in selection bias is not true.

The authors have questioned our fixed NT-pro BNP cut off value and have rightfully advised for usage of age and gender specific cut-offs. Since we were conducting a comparative study of levels in a heterogeneous group (KD patients vs other febrile controls) we thought it to be more convenient to have a single cut-off. Moreover, our study

period was 2019-2020, before these cut-off values were generated in 2022 [2].

The authors have advised to consider KD prevalence in a geographic area when interpreting NT-pro BNP values. We feel that KD prevalence in an area depends on KD awareness, and the conviction of the treating team to accept the diagnosis especially of incomplete KD.

Even in complete KD the individual clinical findings do not throw much light, it is the constellation of the findings that establishes the diagnosis. The diagnosis is, thus, even more difficult in incomplete KD where the entire sets of classical signs are absent. So, we need accessory support for establishing a diagnosis in the incomplete ones. And here lies the importance of markers like NT-pro BNP which might play a role in the diagnostic algorithm.

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2. Kiess A, Green J, Willenberg A, et al. Age-dependent reference values for hs-Troponin T and NT-proBNP and determining factors in a cohort of healthy children (The LIFE Child Study). Pediatr Cardiol. 2022;43:1071-83.

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CLIPPINGS: PEDIATRIC ENDOCRINOLOGY

Emergency department presentations of diabetic ketoacidosis in a large cohort of children (*Pediatric Diabetes. 2023, Article ID 6693226*)

Failure to manage diabetic ketoacidosis (DKA) can be life-threatening. In this study, children from 12 centers aged < 18 y with DKA (glucose > 300 mg/dL, serum pH < 7.25, or serum bicarbonate < 15 mEq/L) enrolled in the Pediatric Emergency Care Applied Research Network (PECARN) Fluid Therapies Under Investigation in DKA (FLUID) Trial were included. Data were also collected for children who presented to the centers during the enrolment period but were not enrolled due to disease or treatment-related reasons. Demographic, clinical, and biochemical findings among children with newly and previously diagnosed diabetes and children in different age groups were compared. Over 5 years study period, total 1553 children had 1679 DKA episodes. Children with newly diagnosed diabetes had 799 (47.5%) episodes and 396 (23.6%) were severe (pH < 7.1). Children < 6 years of age had more severe hypocarbia and higher blood urea nitrogen levels but not severe DKA (pH < 7.1). Thus, they had higher risk for cerebral injury (higher BUN and lower pCO_2) and greater renal dysfunction despite similar levels of acidosis compared to the other age groups. Lower family income and maternal education level were significantly associated with more severe DKA in children with new-onset diabetes, as well as, recurrent DKA in previously diagnosed children. Greater efforts are needed to identify the children with diabetes early and to prevent recurrent DKA, particularly among children in low-SES groups. Young children with DKA may need more intensive monitoring due to higher risk of cerebral injury.

Growth hormone use in pediatric inflammatory bowel disease. (*J Pediatr Endocrinol Metab. 2023;36:1012-7*)

Children with inflammatory bowel disease (IBD) often have poor linear growth. In this retrospective study, researchers reviewed the growth charts of patients with IBD aged 0-21 y from a single centre who received at least 1 year of growth hormone (GH) therapy. The aim of the study was to determine whether GH use in pediatric IBD leads to improved height outcomes. A total of 28 patients (26 with Crohn's disease and 2 with ulcerative colitis) were included. There was a significant mean difference in height z-score from baseline to 1 year on therapy (–2.25 vs –1.50, $P < 0.001$). There was a significant mean difference between the baseline and the final height z-scores in the 19 patients who completed GH therapy (–2.41 vs –0.77, $P < 0.001$). The use of GH use was associated with improved height outcomes as reflected in improved height z-scores both after one year of therapy and at the completion of GH therapy.

Excess body weight and dyslipidemia at well-child visit (*J Pediatr Endocrinol Metab. 2023;36:1037-43*)

In this cross-sectional study, anthropometric data and laboratory results of children aged 2 to 9 y ($n = 363$) attending a pediatric clinic over a period of 3 y were analyzed using logistic and linear regression models. Mean (SD) age of children was 6.3 (2.2) years. 114 children (31.4/%) had excess body weight and 53 (14.6/ %) had obesity/severe obesity. Dyslipidemia was detected in 114 (34.4/%) children and triglycerides were the most frequently altered lipids (18.5/ %), followed by HDL-C (16.8/ %) and LDL-C (9.1/%). One-third of the children had excess body weight and dyslipidemia. Elevations in triglycerides correlated with increase in BMI z-score. With changing lifestyles, these findings reinforce the importance of regular monitoring of the nutritional status in well-child visits and suggests that universal screening for dyslipidemia in children may be needed.

Transdermal blood sampling for C-peptide is a minimally invasive, reliable alternative to venous sampling in children and adults with type 1 diabetes (*Diabetes Care. 2023:dc231379*)

C-peptide and islet autoantibodies are frequently performed in type 1 diabetes (T1D) through venous sampling, which limits its acceptability in children. The researchers assessed a novel transdermal capillary blood (TCB) collection method as a practical alternative to conventional venous sampling in 91 individuals (71 with type 1 diabetes, 20 controls). Plasma C-peptide were measured in participants using contemporaneous venous and TCB sampling. Venous serum and plasma, and TCB plasma were obtained from participants with T1D, for measurement of autoantibodies to glutamate decarboxylase, islet antigen-2, and zinc transporter 8. Venous serum was compared with venous and TCB plasma for detection of autoantibodies using established thresholds. Age-appropriate questionnaire was applied to study the acceptability. TCB C-peptide showed good agreement with venous plasma to detect venous C-peptide ≥ 200 pmol/L. Where venous serum in multiple autoantibody positive TCB plasma agreed in 22 of 32 (sensitivity 69%); comparative specificity was 97% (35 of 36). TCB was preferred to venous sampling (T1D: 63% vs 7%; 30% undecided). Transdermal capillary testing for C-peptide is not only a sensitive and specific but also an acceptable alternative to venous sampling. However, TCB sampling for islet autoantibodies needs further assessment.

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NEWS IN BRIEF

Conservative Oxygenation in Critically Sick Children

Oxygen is one of the commonest supportive treatments in the emergency room. Both hypoxia as well as hyperoxia can have detrimental effects on the human body. Oxy-PICU study, a multicentric, open-label, parallel-group, randomized controlled trial, was conducted in 15 pediatric intensive care units (PICUs) across the United Kingdom, in which researchers compared the effect of liberal (peripheral SpO_2 > 94%) vs conservative oxygenation (peripheral SpO_2 88-92%) on the duration of organ support or death in the 30 days following allocation. 2040 children, aged ≥ 38 weeks corrected gestational age and younger than 16 years, receiving invasive ventilation and supplemental oxygen were allocated into one of the two groups. An intention to treat analysis included the outcome of 1872 children who showed a significantly lower duration of organ support or death in the first 30 days in the children receiving conservative oxygenation (P = 0.04). Authors concluded that widespread adoption of this strategy can help in improving the outcomes of sick children, and reduce the healthcare cost especially in low- and middle-income countries. (*Peters MJ, Gould DW, Ray S, et al; Oxy-PICU Investigators of the Paediatric Critical Care Society Study Group (PCCS-SG). Conservative versus liberal oxygenation targets in critically ill children (Oxy-PICU): a UK multicentre, open, parallel-group, randomised clinical trial. Lancet. 2023 Dec 1:S0140-6736(23)01968-2. Epub ahead of print*)

Ketogenic Diet for Treatment of Infants with Drug Resistant Epilepsy

The ketogenic or keto diet is a specialised dietary approach characterized by high-fat (55-60%), moderate protein (30-35%) and low-carbohydrate (5-10%) of total food intake. A ketogenic diet has been effective in reducing the seizure frequency and drug independence among pediatric and adult patients with difficult to treat epilepsy. As early onset-epilepsies have poor seizure control and association with poor neurodevelopmental outcomes, researchers from United Kingdom studied the efficacy of a classic ketogenic diet at reducing seizure frequency in infants with drug-resistant epilepsy in comparison to antiseizure medicines. A phase 4, open-label, multicenter, randomised clinical trial, recruited 136 infants aged 1–24 months with drug-resistant epilepsy (defined as four or more seizures per week and two or more previous antiseizure medications) from 19 centres across the UK. Participants were allocated to either an intervention group (receiving classic ketogenic diet, n = 78) or control group (receiving further antiseizure medication for 8 weeks, n = 58). After 12 months of follow up, the median (IQR) number of seizures per day during 6-8 weeks was comparable in the ketogenic diet group (5 [IQR 1-16]) and antiseizure medication group (3 [IQR 2-11]; IRR 1·33, 95% CI 0·84-2·11. A ketogenic diet could be used as a safe therapeutic add-on in infants whose seizures continue despite previously trying two antiseizure medications. (*Schoeler NE, Marston L, Lyons L, et al; KIWE study group. Classic ketogenic diet versus further antiseizure medicine in infants with drug-resistant epilepsy (KIWE): A UK, multicentre, open-label, randomised clinical trial. Lancet Neurol. 2023;22:1113-24.*)

Make-in-India Drugs for Rare Diseases in India: Aatmanirbhar Bharat

Rare diseases include genetic disorders, rare cancers, degenerative disorders and infectious tropical diseases, among these genetic disorders is the largest group. Though individually rare, estimates suggest that collectively the number of affected individuals vary between 6% to 8% of the population in any country, and India could have a total of 8.4-19 crore cases of rare diseases. Management of these diseases poses a significant challenge in terms of lack of information about the disease burden, making correct and timely diagnosis, complex tertiary level management involving long term care and rehabilitation, and the non-availability and prohibitive cost of treatment. In 2021, the Ministry of Health and Family Welfare, Government of India, had released the National Policy for Rare Diseases, to develop a national consortium for research and development on therapeutics for rare diseases, with an expanded mandate to include research and development, technology transfer and indigenization of therapeutics. The Ministry of Health and Family Welfare, Government of India, has recently launched the generic version of drugs for the treatment of four rare diseases - Wilson's disease, Gaucher's disease, Tyrosinemia type I and Lennox-Gastaut Syndrome. This step will bring a drastic change in the management of these patients as till now very few of these were receiving the treatment due to issues like regulatory permissions required in the importation, availability of drug and exorbitant cost of these drugs. This step will reduce the cost and thus improve the availability of these drugs not only in India but also in other low- and middle-income countries. (*Dutta SS. First 4 made-in-India drugs for rare diseases launched, 4 more in pipeline, announces govt. The Print. Nov 24, 2024*)

Rising Obesity and Myopia in School-going Children

In a recent health camp organized in 20 Delhi government schools, 22,000 students were assessed wherein their body mass index (BMI), vision and mental health status were evaluated. An alarmingly high prevalence of obesity of 69% among the surveyed children was seen; 15% children had decreased visual acuity. These findings highlight the need of an urgent action to counter the arising pandemic of obesity and myopia in Indian children. (*Gusian B. Over 15,000 students in 'red zone' of BMI in Delhi govt-run schools: Survey. News Nine. Dec 12, 2023. Retrieved from: https://www.news9live.com*)

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REVIEWER INDEX

INDIAN PEDIATRICS

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The present status of this Journal is largely dependent on the expertise and selfless cooperation of the Reviewers, whose help we gratefully acknowledge. We are indebted to them for this service.

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