National Board of Examinations Journal of Medical Sciences
Volume 1, Issue 3, March 2023

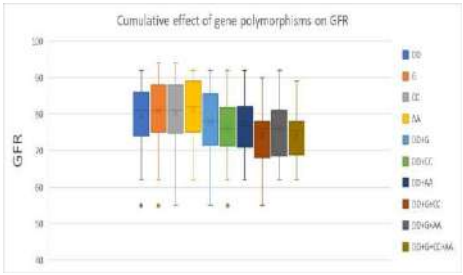
National Board of Examination (NBE)
Journal *of* Medical Sciences

NBEJMS

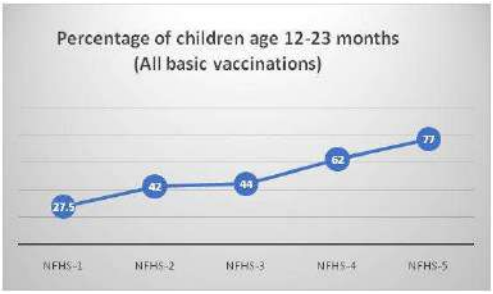
N B E J M S

The average productivity of residents is around 37% of that corresponding to senior physicians

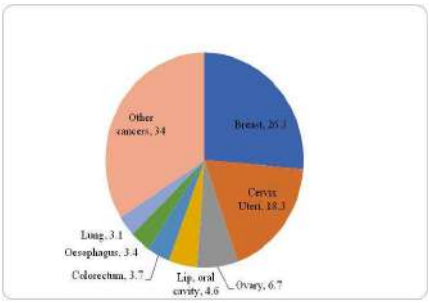
Cumulative effect of Gene Polymorphism on GFR



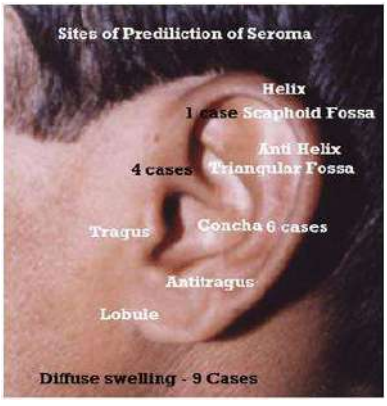
Percentage of children age 12-23 months (All basic vaccination)



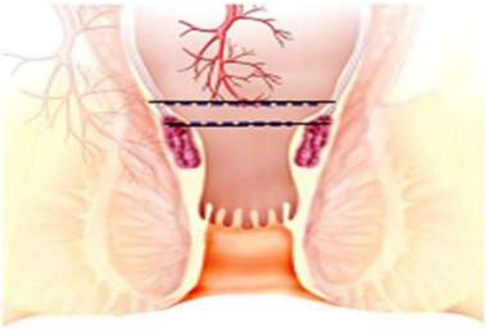
Estimated Cases of Breast diseases in 2020 in India. (females all ages)



Distribution of seroma in Pinna



Hemorrhoidectomy: Two circumferential suture lines



Dr. Chivate's Procedure

NATIONAL BOARD OF EXAMINATIONS – JOURNAL OF MEDICAL SCIENCES

Volume 1 • Issue 3 • March 2023

National Board of Examination - Journal of Medical Sciences
Volume 1, Issue 3, Pages 117–123, March 2023
DOI 10.61770/NBEJMS.2023.v01.i03.001

EDITORIAL

Emergence of India as the Future of Global Health Economy

Minu Bajpai[1] and Abhijat Sheth[2]
[1]*Dean(Academics), Professor & Head, Departments of Paediatric Surgery, All India Institute of Medical Sciences, NewDelhi - 110029, India*
[2]*Senior Consultant, Cardiothoracic Surgeon & C.E.O., Apollo Hospital, Ahmedabad & President, NBEMS*

Accepted: 26-February-2023 / Published Online: 01-March-2023

Expenditure on health: An investment in economic phraseology

An unexpected COVID-19 pandemic underscored the importance of the healthcare sector and its inseparable link with other major sectors of the economy. The pandemic also unmasked the vulnerability of healthcare crisis to spiral economic consequences. Not alone to counter any future pandemics, India's healthcare system needs to be constructive & agile. As private sector is the leading healthcare provider in India, it remains critical for developing policies that mitigate information asymmetry in healthcare system. An increase in public spend from 1 percent to 2.5–3 percent of GDP can decrease the Out-Of-Pocket Expenditures from 65 per cent to 30 per cent of overall healthcare spend [1]. The health of a nation depends critically on its citizens having access to an equitable, affordable and accountable healthcare system. Health affects domestic & economic growth directly through labour, productivity and the economic burden of illnesses [2].

*Corresponding author: Minu Bajpai
E-mail address: bajpai2b@gmail.com

Increasing life expectancy from 50 to 70 years (a 40 percent increase) could raise the economic growth rate by 1.4 percentage points per year. Life expectancy in a country correlates positively with per-capita public health expenditure. Increased prioritization of healthcare in the central and state budgets is important as it crucially impacts how much protection citizens get against financial hardships due to out-of-pocket payments made for healthcare [3].

Finally, the role of the government is to formulate policies, services, and manage activities. It should be collaborative between health and the sectors other than health, to develop a partnership. This would enable better service delivery based on the comparative advantages of each relevant sector, such as, the private, including, corporate hospitals. It would also include, nongovernmental organizations particularly based in the community, academia and medical colleges and research organizations.

This is the time for the expansion of telemedicine and digital health industry in the

country. These factors, together, can boost the healthcare industry advantageous for investment. The expansion of private hospital to Tier 2 and Tier 3 locations, beyond metro cities, offers an attractive investment opportunity. The Ministry of Chemicals and Fertilizers, Department of Pharmaceuticals have taken several steps such as Scheme for Strengthening of Pharmaceuticals Industry (SPI), Production Linked Incentive (PLI) scheme for Pharmaceuticals, PLI Scheme for Promotion of Domestic Manufacturing of critical Key Starting Materials (KSMs)/Drug Intermediates and Active Pharmaceutical Ingredients (APIs) in the Country. PLI Scheme for the promotion of Domestic Manufacturing of Medical Devices has boosted the domestic manufacturing of pharmaceuticals, alongside offering investment avenues in segments like synthesis and evaluation, drug development, drug delivery, collaborative manufacturing and evidence based research, vaccine development, etc. It has provided opportunities in medical devices industry, with expansion of diagnostic and pathology centres [4].

Universal health coverage (UCH) is an investment in human capital and a foundational driver of inclusive and sustainable economic growth and development. It is a way to support people so they can reach their full potential and fulfil their aspirations.

The UHC global monitoring report 2017 reveals that at least half the world's population still lacks access to essential health services. Furthermore, some 800 million people spend more than 10 per cent of their household budget on health care, and almost 100 million people are pushed into extreme poverty each year because of out-of-pocket health expenses.[5]

The present structure of Indian healthcare industry

The Indian healthcare industry is growing at a compound annual growth rate (CAGR) of 22% during 2016–22 with a target to achieve US$ 372 billion in 2022. Healthcare industry has become the largest sector of the Indian economy and providing direct employment to approx. 47 lakhs peoples. As per the estimate by the National Skill Development Corporation (NSDC) healthcare can generate 27 lakhs additional jobs in India [5].

In fact, economic historians estimate that improved health accounted for about one-third of the overall GDP-per-capita growth of developed economies in the past century [6,7].

Poor health costs each year 15% global GDP due to premature deaths & lost productive potential in working age. In India, there has been significant improvements in the recent past. however, the fast population growth in India, which is expanding at both its ends- high birth rate & increase in elderly population from 3.8% to 6.6%, is what we need to address.

Health continues to have the potential to stimulate growth

With improved health, there would be a decline in premature deaths, resulting thereby in an increase in the working-age population. When people are healthier, absences from sickness decline, and workers are less distracted.

Sizing up the economic impact of better health, Penn, et al, found that it could add $12 trillion to global GDP in 2040—an 8 percent boost, or 0.4 percent a year faster growth. These gains could not only help the economic recovery from the COVID-19 pandemic but also, over the longer term, counter demographic headwinds from an aging population [8].

Strategies to prevent chronic diseases can significantly impact economic outcomes in enlarging the pool of healthy individuals beyond 65 years of age. Thus, it would naturally expand the available labour force potential within an age range of 20 to 65 years.

In Germany, a change in healthcare policy from cure to prevention had been envisaged to create a large labour force potential between 2002 and 2050.

Expenditure on health and education, therefore, must be considered an investment in economic phraseology. The resultant change, would be reflected when importance is given to prevention and control of risk factors for chronic diseases which is similar to that for prevention and control of infectious diseases.

Based on type of services, the market can be stratified into in-patient services and out-patient services.

In financial year 2021 the in-patient services share has been around 55.29%. Post-Covid, there has been a realization for pro-active treatment towards prevention of disease & wellness. By financial year 2027 outpatient services are likely to outgrow this segment. With patients looking for 'One-Hop shopping' multi-specialty hospital chains would mushroom in numbers.

In patient bed space would be utilized more and more for critical care admissions. Envisaging the upcoming National needs, the National Board of Examinations in Medical Sciences (NBEMS) has introduced a 6 year course in Critical Care and a 2 years course in Diploma in Emergency medicine.

Healthcare market in India is expected to reach US$ 372 billion by 2022, driven by rising income, better health awareness, lifestyle diseases and increasing access to insurance. The Indian hospital industry alone, accounting for 80% of the total healthcare market, is expected to touch US$ 132 billion by 2023. As of 2021, the Indian healthcare sector is one of India's largest employers as it employs a total of 4.7 million people [4].

Healthcare industry functions through two segments. These are:

A. Hospital (government and private)
B. The 'Second' health sector

The increasing demand for new products and services will create a second health care sector. This sector deals with the following:

1. Diagnostics and Interventions (imaging and laboratory investigation)
2. Pharma (synthesis, evaluation, extraction, toxicology, purification, processing, manufacturing, packaging and distribution of medications and vaccines),
3. Devices and Equipments (manufacturing and establishment of medical equipments, devices, instruments etc.),
4. Health insurance,
5. Research,
6. Digital health programme (telemedicine) and
7. Medical tourism.

Timing, Scope and the Opportunity

India has large, almost one-fifth of global population that required continued growth of healthcare sector. By 2035, 1090 lakh people prone to develop diabetes, would make India a 'diabetic capital of the world' [9]. An increasing

pattern of middle class now able to spend on healthcare is also ready to adopt insurance support for greater spending. A gradual rise of elderly people (over 65) from the current 6% per cent to 13% by 2050, will boost the number of age-related ailments and demand for aged care [10].

The Indian market is growing with the pace 15% annually and stands at $7.5 billion, of which 77% is imported [11]. India has second largest nutraceutical market after China and turns out to be raising source of business by 2030 [12].

Reforms and Opportunities

Rising demand

- Rising income and affordability.
- Growing elderly population, changing disease patterns.
- Rise in medical tourism.
- Better awareness of wellness, preventive care and diagnosis.

Focus

- Expanding R&D and distribution facilities in India.
- Use of modern technology.
- Providing support to global projects from India.

Support

- Encouraging policies for FDI in the private sector.
- Reduction in customs duty and other taxes on life-saving equipment.
- NRHM allocated US$ 10 billion for healthcare facilities.
- National Health Insurance Mission to cover entire population.

Policy support and government initiatives

Pradhan Mantri Jan Arogya Yojana (PMJAY)

- The government announced Rs. 64,180 crore (US$8.80 billion) outlay for the healthcare sector over six years in the Union Budget 2021–22 to strengthen the existing 'National Health Mission' by developing capacities of primary, secondary and tertiary care, healthcare systems, and institutions for detection and cure of new & emerging diseases.

Tax incentives

- All healthcare education and training services are exempted from service tax.
- Increase in tax holiday under section 80-IB for private healthcare providers in non-metros for minimum of 50 bedded hospitals.
- 250% deduction for approved expenditure incurred on operating technology enables healthcare services such as telemedicine and remote radiology.
- Artificial heart is exempted from basic custom duty of 5%.
- Income tax exemption for 15 years for domestically manufactured medical technology products.
- The benefit of section 80-IB has been extended to new hospitals with 100 beds or more that are set up in rural areas. Such hospitals are entitled to 100% deduction on profits for 5 years [13].

Training of Doctors: Catching up with the 'Core Dimension'

The core dimension of health care industry is Training of DOCTORs. In a study, the finding showed that the overall contribution of resident physicians to hospitals' production allows considering them as an input in most cases. In particular, their average productivity is around 37% of that corresponding to senior physicians [14] (Figure 1).

The core dimension of health care industry is Training of DOCTORs.

In a study, the finding showed that the overall contribution of resident physicians to hospitals' production allows considering them as an input in most cases. In particular, their average productivity is around 37% of that corresponding to senior physicians [16].

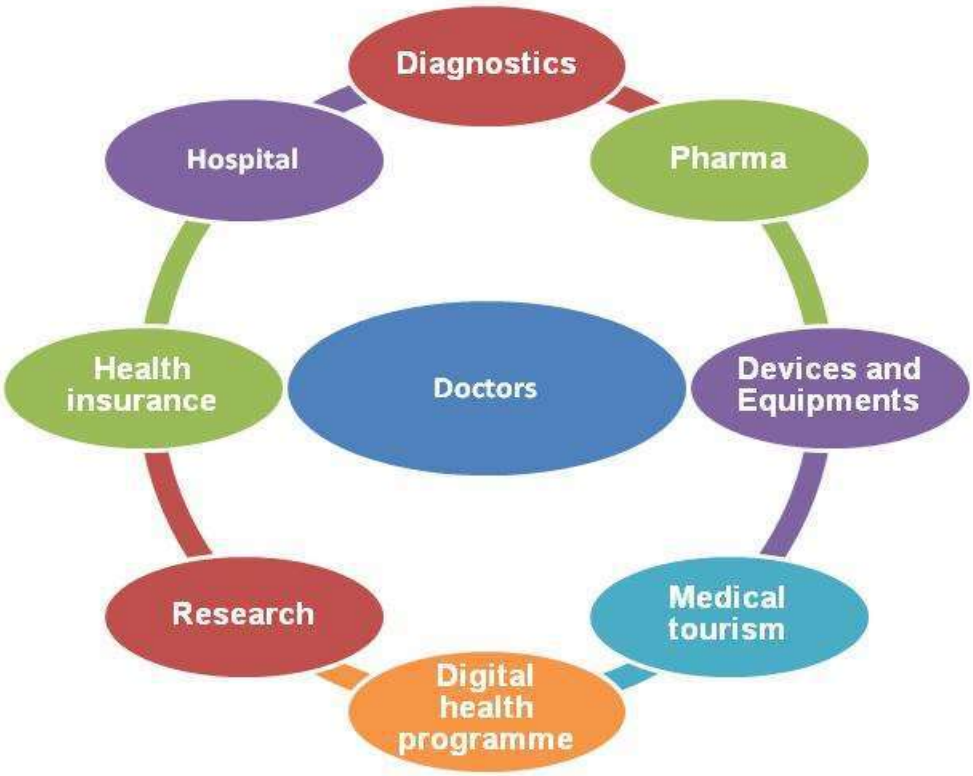


Figure 1. Training of Doctors: Catching up with the 'Core Dimension'

The NBEMS contributing 13,560 seats of 99 specialized post-graduate programme in its 1,209 accredited institutions/hospitals (415 government and 794 private) opens the opportunities for doctors practicing in either government or a private hospitals to becoming trainers and participate actively in training of doctors. This role will be emphasised with the incorporation of "Training of Doctors" as a key attribute by the NBEMS. Teaching and training should be an integral part of the role of the senior doctors serving as consultants.

The NBEMS "Training of Doctors" programme clearly states that all consultants have a professional obligation to contribute to the education and training of students persuing any professional course run by the NBEMS. Every consultant should be prepared to oversee the progress of the students not only as an issue of professional obligation, but to impart training which ensures safe care [15].

Conclusion

In terms of revenue and employment, the Indian healthcare industry is one of the

largest economic sector among others. We are emerging as fastest growing economy with several opportunities for investment. We have elaborated the growth potential and investment opportunity in healthcare sector, including insights about its employment generation potential, overarching policy landscape, enabling policies and investment opportunities in hospitals and infrastructure, drug and vaccine development, medical devices, medical tourism, digital healthcare industry with telemedicine and health insurance. India's competitive advantage lies in its large pool of well-trained medical professionals. India is also cost competitive compared to its peers in Asia and western countries. The low cost of medical services has resulted in a rise in the country's medical tourism, attracting patients from across the world. Moreover, India has emerged as a hub for R&D activities for international players due to its relatively low cost of clinical research.

With patients looking for 'One-Hop shopping' multi-specialty hospital chains are likely to outgrow in-patient services. The bed space would be utilized more and more for critical care admissions. Envisaging the upcoming National needs, the National Board of Examinations in Medical Sciences (NBEMS) has introduced a 6 year course in Critical Care and a 2 years course in Diploma in Emergency medicine.

The core dimension of health care industry is Training of DOCTORs. The average productivity of residents is around 37% of that corresponding to senior physicians.

Conflicts of interest

The authors declares that they do not have conflict of interest.

References

1. National Health Policy 2017 (Ministry of Health and Family Welfare). https://www.nhp.gov.in/nhpfiles/national_health_policy_2017.pdf
2. Tammy Boyce and Chris Brown. Economic and SOCIAL impacts and benefits of health systems. https://apps.who.int/iris/bitstream/handle/10665/329683/9789289053952-eng.pdf. (WHO Repot 2004)
3. WHO Director General. The World Health Report 2010. https://www.who.int/director-general/speeches/detail/the-world-health-report-2010
4. Business Finance. Indian healthcare sector to surge threefold at a CAGR of 22% during 2016-2022: Minister of Chemicals & Fertilizers. *Powered by* Capital Market - Live News. Capital Market. Business Standard. Sept, 2019
5. Tracking Universal Health Coverage: 2017 Global Monitoring https://apps.who.int/iris/bitstream/handle/10665/259817/9789241513555-eng.pdf)
6. Based on estimates from Suchit Arora and Robert W. Fogel. See Suchit Arora, "Health, human productivity, and long-term economic growth," *Journal of Economic History*, September 2001; 61(3):699–749.
7. Robert W. Fogel, "Health, nutrition, and economic growth," *Economic Development and Cultural Change*, April 2004, Volume 52, Number 3, pp. 643–58, journals.uchicago.edu.
8. Penelope Dash, Grail Dorling, Katherine Linzer, Aditi Ramdorai, Jaana Remes, Kristin-Anne Rutter, and Shubham Singhal. How prioritizing health could help rebuild economies. McKinsey Global Institute. McKinsey Centre for Government. Updated April 30, 2020 (©2020 McKinsey & Company)

9. Sanjay Basu. By 2035, 98 million Indian could have diabetes. India needs traditional diet. Times Evoke, Times of India. January 8, 2022.
10. Ageing and Health, WHO Fact Sheet, October 1, 2022. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health
11. Medical Device. IBEF Report 2022. India Brand Equity Foundation. August 2022 https://www.ibef.org/industry/medical-devices#
12. Rajat Yadav, Radhika Mehta Malik. The Growing Nutraceutical Market in India. Invest India. National Investment and Promotion and Facilitation Agency. January 10, 2020.
13. Govt plans Rs. 50,000 crore programme to boost health infrastructure: Report. India Brand Equity Foundation. June 17, 2021 https://www.ibef.org/news/govt-plans-rs-50000-crore-programme-to-boost-health-infrastructure-report.
14. Perez-Villadóniga, M.J., Rodriguez-Alvarez, A. and Roibas, D. The contribution of resident physicians to hospital productivity. Eur J Health Econ 2022;23:301–312.
15. Minu Bajpai, Abhijat Sheth, Rakesh Sharma, Anurag Agarwal, Dinesh Chand, N. Iboyaima Mangang, Vinay Gupta, Richa Raju, N. Rashmi Raj N, Devender and Sandhya. National Board of Examination in Medical Sciences (NBEMS): Current and Future Trajectories — Part–1. National Board Journal of Medical Sciences. 2023; 1(1):1–11.
16. Maria J. The European Journal of Health Economics. 2022;23:301–312.

National Board of Examination - Journal of Medical Sciences

Volume 1, Issue 3, Pages 124–134, March 2023

DOI 10.61770/NBEJMS.2023.v01.i03.002

ORIGINAL ARTICLE

Role of RAAS pathway gene polymorphisms in congenital uropathies

Ankur Bhardwaj,[1] Minu Bajpai,[1] Sachit Anand,[1] Prabudh Goel,[1] Kalpana Luthra,[2] Anjali Pandey,[3] and Alok Kumar[4]

[1]*Departments of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi - 110029, India*

[2]*Department of Biochemistry, All India Institute of Medical Sciences, New Delhi - 110029, India*

[3]*Departments of Biostatistics, All India Institute of Medical Sciences, New Delhi - 110029, India*

[4]*Centre for Community Medicine, All India Institute of Medical Sciences, New Delhi - 110029, India*

Accepted: 19-October 2022 / Published Online: 01-March-2023

Abstract

Aims: To study the prevalence of gene polymorphisms of RAS pathway genes in children with Congenital Anomalies of kidney and urinary tract (CAKUT) and evaluate their role in the outcome.

Material and Methods: A cross sectional study was done in 250 children (<14 yr) with CAKUT and 150 controls over a period of 3 years (2019–2021). Three diseases namely Posterior Urethral Valve (PUV), Vesico ureteric reflux (VUR) and Pelvic ureteric junction obstruction (PUJO) were selected. Polymorphism of 4 genes of RAAS pathway-AGT, AT2R, AT1R and ACE was assessed in blood samples of subjects. Polymorphism frequency was analysed with respect to clinical and radiological outcomes. Patients were followed over a period of 1 year to evaluate the role of gene polymorphisms in disease progression.

Results: While comparing the polymorphism frequencies in cases and controls, we found that disease alleles of all 4 genes were over represented in the case group and significant association was seen with 2 genes-AT2R (p = 0.03) and AT1R (p = 0.02). Multivariate analysis showed that odds of getting CAKUT were higher with following genotypes namely ACE DD (+0.5 times), AT2R (+0.4 times), AT1R AC (+1.6 times) and AGT CC (=0.6 times). Progressive deteriorators formed 22% of the cases, more seen in PUV patients. Sub group analysis of progressive deteriorators showed that AT2R G allele and ACE DD allele increased the odds of progressive deterioration by 7 and 14 times respectively. Cumulative effect of pathogenic alleles of different RAS genes showed that co existence of DD alleles with other alleles had the most serious outcomes, thus raising the possibility of synergism like a 'second hit'.

Conclusion: Almost 1/4th of children with CAKUT deteriorated despite getting the adequate treatment. Our studies found significant association of ACE and AT2R gene polymorphisms with incidence and progression of congenital uropathies.

*Corresponding author: Minu Bajpai
Email: bajpai2b@gmail.com

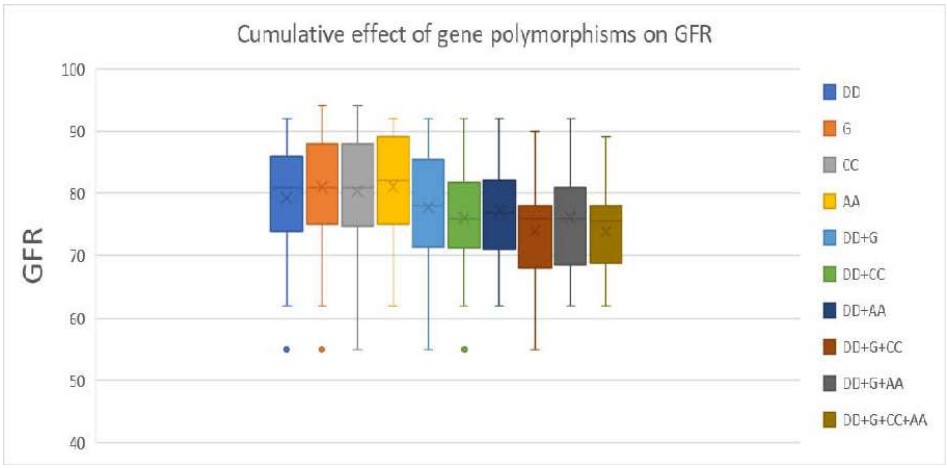
Graphical Abstract

Role of RAAS pathway gene polymorphisms in congenital uropathies

Aim
To study the prevalence of gene polymorphisms of RAS pathway genes in children with Congenital Anomalies of kidney and urinary tract (CAKUT) and evaluate their role in the outcome.

Methods
A cross sectional study was done in 250 children (<14 yr) with CAKUT and 150 controls over a period of 3 years (2019–2021). Three diseases namely Posterior Urethral Valve (PUV), Vesico ureteric reflux (VUR) and Pelvic ureteric junction obstruction (PUJO) were selected.

Results



Conclusions
Almost 1/4th of children with CAKUT deteriorated despite getting the adequate treatment. Our studies found significant association of ACE and AT2R gene polymorphisms with incidence and progression of congenital uropathies.

A. Bhardwaj, M. Bajpai et al.

Introduction

Congenital anomalies of Kidney and Urinary tract (CAKUT) includes a wide spectrum of anomalies including Kidney anomalies (agenesis, hypoplasia, dysplasia), ureteric anomalies (PUJ obstruction, duplex ureter), Vesico ureteric junction and many others [1]. Though the umbrella of CAKUT seems to be quite wide, many of the diseases are co existing and thus related in their pathogenesis.

Prevalence of CAKUT is 3-6 per 1000 live births accounting for almost 20-30% of congenital anomalies [2,3]. It is the most common cause of CKD (34–59%) and End stage renal disease in children (31%) [2,4–6]. Almost all children with ESRD require renal replacement therapy. CKD and the need for RRT in childhood lead to severe impairment of physical and psychosocial development [7-9]. All these consequences demand for intense experimental and clinical research for new diagnostic, preventive and therapeutic options to improve outcome of this disorder.

One intricate problem with this group of anomalies is that the renal damage starts during intra uterine period and goes on in some patients despite starting the best treatment at the correct time. A lot of research has been done in the past 2 decades to decode this mystery of progressive deterioration in CAKUT in children. Many risk factors including biochemical markers and genetic alterations have been proposed to predict early kidney injury in CAKUT. “ICMR Centre for Research on Congenital uropathies”, AIIMS, New Delhi has been working in this area for last 25 years. Multiple projects done have revealed the role of Plasma renin activity, Gene polymorphism, Urine bio markers- microalbuminuria, NGAL in pathogenesis of CAKUT [10–21].

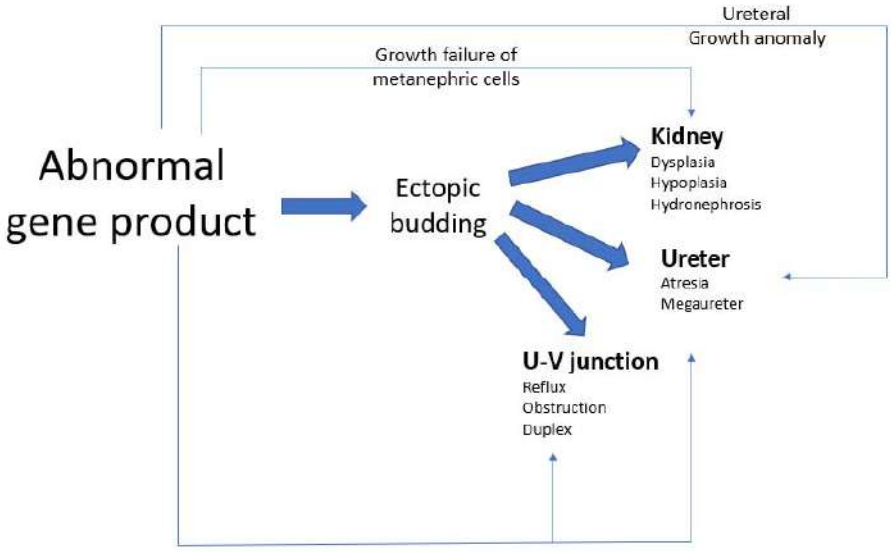


Figure 1: Overview of mechanism of CAKUT [1]
(Figure 1 is adapted from Kidney International, Vol.61 (2002), Ichikawa I, Kuwayama F, Pope IV JC, Stephens FD, Miyazaki Y. Paradigm shift from classic anatomic theories to contemporary cell biological views of CAKUT, pp.889-898, © 2002, with permission from elseiver)

Genetic predisposition to CAKUT is supported by concurrence of these anomalies with multi organ defects and frequency of familial cases (~10%) [22]. Around 2900 genes are involved in nephrogenesis but polymorphisms have been identified in less than 100 till now [23]. The notion that CAKUT may be caused by single gene mutations is suggested by 3 findings [1]. Familial aggregation of defects like VUR, MCDK, Duplex ureters [2] Monogenic mouse models exhibit CAKUT phenotypes [3] Human multi organ monogenic syndromes may include CAKUT phenotypes [22]. This notion was corroborated by discovery of >20 single nucleotide polymorphisms (SNPs) as a cause of CAKUT in humans [2,9,24–26].

Table 1. Important genes involved in human CAKUT are tabulated as below [22, 27]

S. No.	Gene	CAKUT
1	PAX2	Agenesis, hypoplasia, Renal coloboma syndrome, VUR
2	HNF1 β	Renal cysts/dysplasia and diabetes, Single kidney, Horse shoe kidney
3	BMP4	Renal hypo dysplasia, cleft lip, micro ophthalmia, duplex ureters
4	ACE	Renal tubular dysgenesis, hypodysplasia due to PUV, Pulmonary hypoplasia, skull abnormalities
5	AT2R	PUJO, Megaureter, MCDK, PUV
6	SIX5	Branchio oto renal syndrome
7	AGT	Renal tubular dysgenesis
8	AT1R	RTD, PUV
9	WNT4	Renal hypodysplasia, Mullerian aplasia, hyperandrogenism
10	ROBO2	VUR, Duplex ureters
11	CYP11B2	ESRD

Role of RAS (renin angiotensin system) is very important in nephrogenesis and progression of congenital uropathies. Developing mammalian metanephros expresses all components of RAS at various stages of embryogenesis. Mutations in genes encoding components of the RAS in mice cause diverse forms of CAKUT which include hydronephrosis, hypoplastic medulla & papilla,

marked thickening of renal arterial walls and vesico ureteric reflux [27]. Initial role of RAS in nephrogenesis was provided by findings that use of ACE inhibitors or AT-1 antagonists cause fetal anuria leading to oligohydramnios [28,29]. Genes like AT2R, AT1R have been implicated in normal embryogenesis too [23]. Genes like ACE I/D have been implicated in progression of various CAKUT [19,30].

Gene polymorphism means when there is variation of alleles in the population. It differs from the term mutation in that the frequency of variation is >1% in case of polymorphism. Multiple studies have been done to study gene polymorphism in adults with stroke, ESRD and pre eclampsia. Similar gene polymorphism studies in CAKUT have been done in the last 2 decades [31–37].

In this work, we have tried to analyse the role of RAAS genes polymorphism in prevalence and progression of CAKUT. Our aim behind this project was to find out genetic risk factors which will help in risk stratification in children with CAKUT.

Methods

A cross sectional study was carried out in Dept of Paediatric Surgery, AIIMS, New Delhi over a period of 3 years (2019–2021) in children with CAKUT. We chose 3 common congenital uropathies for our study i.e Posterior urethral valves (PUV), Vesico ureteric reflux (VUR) and PUJO (Pelvic ureteric junction obstruction). We chose 4 genes of RAAS pathway for our study- ACE (angiotensin converting enzyme), AT2R (Angiotensin type 2 receptor), AT1R (Angiotensin type 1 receptor) and AGT (angiotensinogen). Since AT2R gene is present on sex chromosome only male population was considered for comparison. 250 Children of <14yrs age were chosen for our study in a random manner from the group of our pediatric urology clinic patients. 150 children without CAKUT were chosen for comparing the prevalence of RAAS gene polymorphisms. These children were selected from our pediatric surgery ward who had non genito urinary illnesses. We also followed 250 children with CAKUT over a period of minimum 1 year to check for progressive deterioration in kidney functions. Deterioration in kidney functions was assessed in terms of ↓GFR, Increase in kidney scars, ↓ in slit renal function (PUJO). A subgroup analysis of gene polymorphisms was carried out in the group of progressive deteriorators.

Methodology for assessing gene polymorphism was as follows: Primers for specific mutations were designed after literature search and with the help of NCBI gene database.

Table 2: Primer sequences & Thermocycling protocols

	Primer sequences	Thermocycling protocol
ACE I/D	5'-CTGAGACCACTCCCATC-3' 5'-GATGTGGCCATCACATTCGTCAGAT-3'	940c for 2min ×cycles , 940c for 15s × cycles , 580c for 10s×cycles , 720c for 30s ×cycles
AT2R	5'-GGATGAACTTCGTTTTTCCTGTTT-3' 5'-GCAGTTATCATAAATCAGCTTGCTTAGT-3'	940c for 2min ×cycles , 940c for 15s × cycles , 590c for 10s×cycles , 720c for 30s ×cycles
AGT rs699	5'-GTG CTG TCC ACA CTG GCT CCC-3' 5'-AAGAACTGCACCTCCCGGCTGGATG-3'	940c for 2min ×cycles , 940c for 15s × cycles , 590c for 10s×cycles , 720c for 30s ×cycles
AT1R rs5186	5'-GCAGCACTTCACTACCAAATGAGCC-3' 5'-CTCATCTCCTGTTGCTCCTCTAACG-3'	940c for 2min ×cycles , 940c for 15s × cycles , 580c for 10s×cycles , 720c for 30s ×cycles

2 ml of peripheral blood sample was collected. DNA was extracted by Key gen extraction kit. Normal and mutant ARMS premixes were prepared according to previously published PCR guidelines. Premixes containing Taq polymerase were kept in thermocycler. PCR products were run by gel electrophoresis. Bands were assessed in UV light and depending on the base pair length, results were analysed.

Clinical and imaging details were taken from pediatric urology clinics records. GFR was measured by plasma sample method. Kidney scars were assessed in DMSA. Split renal function was assessed in PUJO patients with the help of LLEC scan. Outcome variables were gene polymorphism frequencies in CAKUT and non CAKUT patients and Base line GFR, renal scarring and Split renal function at presentation and 1 year. Progressive

deterioration was defined as GFR<60 or ↑se in renal scars or ↓se in SRF by ≥ 10%.

Data extraction was done using Microsoft Excel. Data analysis was done using Stata 12.0. Categorical variables were analysed using t-test and continuous variables were analysed using Pearson/Spearman co relation coefficient. Categorical variables were analysed using Chi-square test. Multi variate analysis was done by logistic regression. A p-value of <0.05 was considered statistically significant.

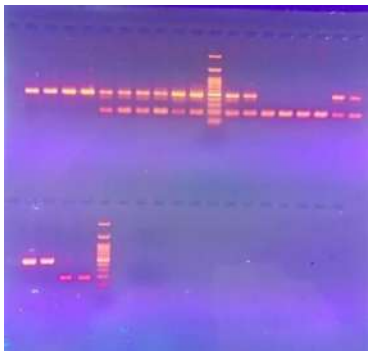


Figure 2. DNA bands on agarose gel under UV light

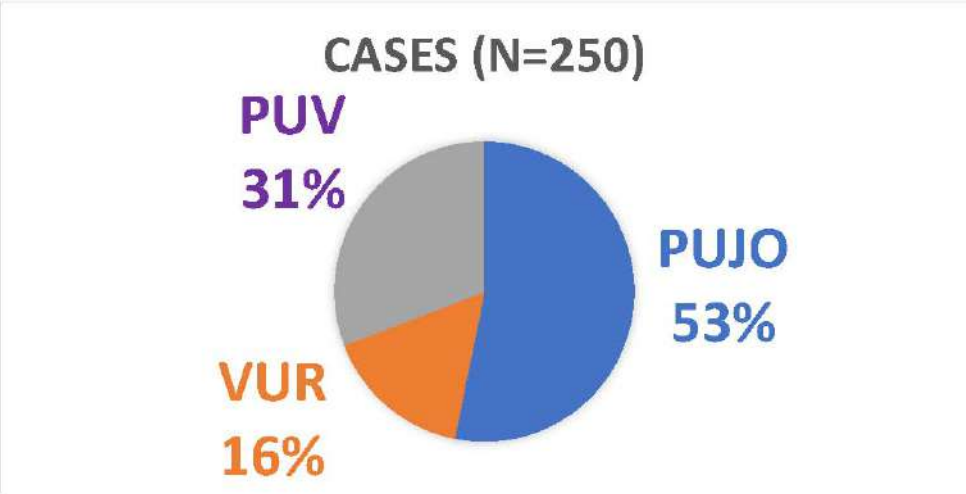


Figure 3: Distribution of 3 anomalies in cases

Results

Distribution of 3 anomalies in CAKUT population was as shown in Figure 3.

We checked for confounding factors like age, sex etc in CAKUT and non CAKUT children and found the 2 populations matching. Average age in CAKUT children was

To check the effect of sex of the child on gene polymorphism frequencies and renal outcomes variables, comparison was done within CAKUT population. No significant differences were found in males and females.

Then we compared gene polymorphism frequencies in CAKUT and non CAKUT children. G allele of AT2R gene, AC allele of AT2R, DD allele of ACE and AA allele of AGT were over represented in CAKUT population. Significant differences were noted in allelic frequencies of AT2R ($p = 0.03$) and AT1R ($p = 0.004$).

Table 3: Distribution of genotype frequencies in cases and controls

Genes	Genotype	CAKUT (*n*=250) (*n*=191 for AT2R)	Controls(*n*=150) (*n*=119 for AT2R)	*p* value
ACE I/D	DD	95	45	0.147
	II	106	65	
	ID	49	40	
AT1R	AA	101	59	0.004
	AC	114	51	
	CC	35	40	
AT2R	A	76	62	0.031
	G	116	57	
AGT	AA	60	46	094
	AC	100	65	
	CC	90	39	

Univariate and multivariate analysis was done to assess the odds of getting CAKUT with pathogenic alleles. It was found that ODDs of getting CAKUT increased with following allelic distribution- ACE DD (+0.5 times), AT2R G (+0.4 times), AT1R AC (+1.6 times) and AGT CC (+0.6 times).

Table 4: Odds ratio of prevalence of CAKUT w.r.t genotypes

	Genotype	Odds ratio (univariate analysis)	Adjusted odds (multivariate analysis)
ACE I/D	DD	1.29	1.90
	II	1	1.40
	ID	0.75	1
AT1R	AA	1	1.94
	AC	1.3	2.66
	CC	0.5	1
AT2R	A	0.6	–*
	G(ref)	1	
AGT	AA	1	1
	AC	1.17	1.15
	CC	1.76	1.6

*Multivariate analysis not possible as AT2R was checked in males only.

To assess the distribution of gene polymorphism with respect to 3 uropathies, we compared the allelic distributions in children with PUJO, PUV, VUR with respect to non CAKUT children. Children with PUJO had significant differences in allele distribution of AT2R gene (p=0.01). ACE gene allelic distribution was significantly different in children with PUV (p=0.03). In sub group of children with VUR, no significant differences were found.

After comparing CAKUT and non CAKUT children, sub group of CAKUT children was studied for renal function variables to find out the mischievous population of progressive deteriorators.

Baseline GFR at presentation was found to be in children with PUV (75ml/min/1.73m^2). Renal scars were found in 1/3rd of children with PUV and VUR. On the other hand, only 1/6th of PUJO population had renal scars.

When renal function variables were assessed over a period of 1 year, progressive deterioration was noted in 32% of PUV patients and 20–25% in PUJO and VUR patients.

Gene polymorphism was studied in this subgroup of progressive deteriorators and results were astonishing. There were significant differences in allelic distributions of all 4 genes- ACE (p<0.001), AT2R (<0.01), AT1R (<0.009), AGT (<0.001).

Table 5: Distribution of genotype frequencies in 'Progressive deteriorators'

	Genotype	Case (n=56) (n=51 for AT2R)	Controls(n=150) (n=119 for AT2R)	P -value
ACE I/D	DD	49	45	<0.0
	II	3	65	01
	ID	4	40	
AT2R	A	10	62	<0.0
	G	41	57	01
AT1R	AA	33	59	0.009
	AC	18	51	
	CC	5	40	
AGT	AA	10	46	<0.0
	AC	13	65	01
	CC	33	39	

ODDs of progressive deterioration with pathogenic alleles were assessed by multivariate analysis. We found that presence of DD allele and G allele increased the odds of progressive deterioration by 14 and 7 times respectively. While rest of the 2 genes increased the odds minimally.

Table 6: Odds of Progressive deterioration w.r.t genotypes

	Genotype	Odds ratio (univariate analysis)	Adjusted odds (multivariate analysis)
ACE I/D	DD	17	0.45
	II	1	1
	ID	0.44	14.2
AT1R	AA	1	1
	AC	0.74	0.72
	CC	2.89	0.43
AT2R	A	1	-*
	G	7.39	
AGT	AA	1	1
	AC	1.17	0.72
	CC	1.76	0.43

Cumulative effect of pathogenic alleles was assessed by comparing frequencies of pathogenic alleles with respect to GFR in children. And we found co-existence of DD allele (ACE gene) with other pathogenic alleles had led to further decrease in GFR.

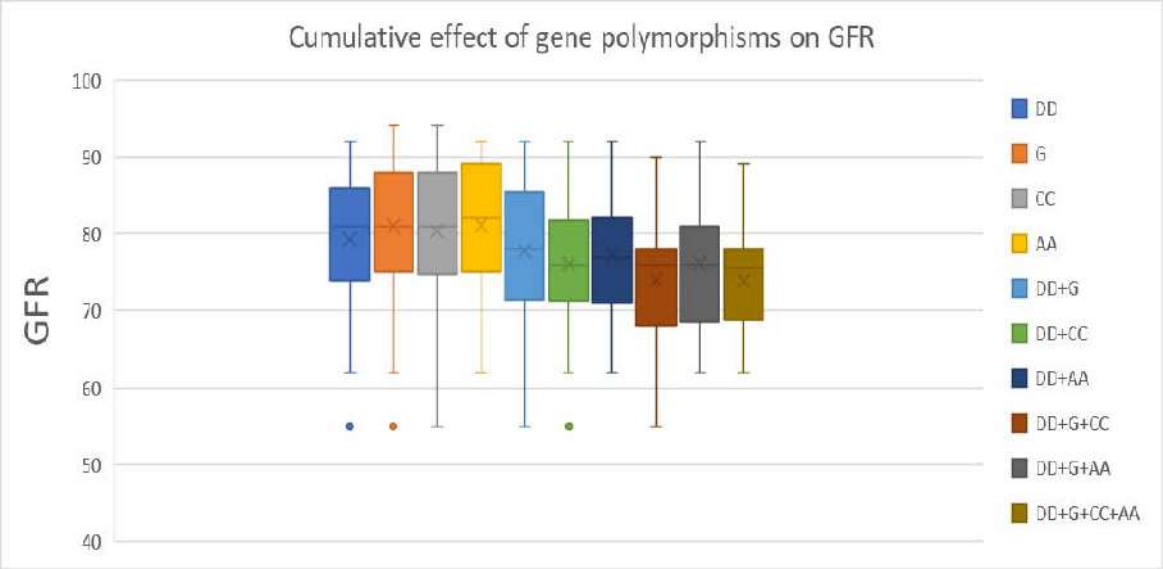


Figure 4: Cumulative effect of different pathogenic alleles

Discussion

Distribution of anomalies in our study was different than distribution mentioned in standard textbooks. Incidence of PUJO, PUV and VUR has been given as 1 in 1250, 1in 6000 and 1 in 100 (38). In our study, incidence of PUJO and VUR was lower than expectations i.e 53% and 16% respectively. Possible cause may be because they are diagnosed late as symptoms are vague and appear late in these 2 anomalies.

While comparing polymorphisms in total cases and controls, although the disease alleles of all 4 genes were over represented in CAKUT population but significant association was seen in 2 genes- AT2R and AT1R. Multivariate analysis showed that odds of getting CAKUT increased in all 4 pathogenic alleles – ACE DD (+0.5 times), AT2R G (+0.4 times), AT1R AC (+1.6times), AGT CC (+0.6 times).

AT2R gene polymorphism has been frequently found to be associated with kidney diseases in both adults and children. Hohenfeller et al, Rigoli et al and Nishimura et al have independently shown in their studies the significant association of AT2R with CAKUT in children [34,37]. High expression of AT2R place this gene amongst the list of important nephrogenic genes. Like other studies, association was seen in subgroup analysis of PUJO patients. But no significant association was seen in PUV or VUR patients. Narsimhan et al studied ACE I/D and AT2R(1332G) gene polymorphisms in 120 children of PUV in 2010. They found that ACE DD alleles and AT2R G alleles were significantly related individually to disease progression in CAKUT. They further that co existence of DD and G allele increased the risk to 3 times [39]. Our study has analysed 2 more genes -AT1R and AGT in a larger population. 2 more anomalies- PUJO and VUR have been included. GFR has been measured by plasma sampling method to give more accurate assessment of renal functions.

AT1R gene polymorphism has been found to be significantly associated with stroke, ESRD, preeclampsia in few studies in adult Caucasian patients (40-42). Our study revealed the role of AT1R AA alleles in prevalence of CAKUT overall and PUJO specifically. Allelic distribution differences were found to be significant in progressive deteriorators. Ours was the first study to study AT1R gen in CAKUT in Indian children thus setting the course for future generations.

Multiple studies by Bajpai et al, Rigoli et al, Livoti et al have reported the of DD allele ACE gene in progressive deterioration of kidney [19,34,43]. Similar results were seen in our study. But we noticed 3 new findings regarding this allele. Firstly, it was not associated with anomalies when their total incidence at presentation was analysed. But on follow up, they played an important role in renal damage thus emphasising the difference in 2 processes i.e nephrogenesis prenatally and progressive deterioration postnatally. Multi variate analysis to assess individual contribution of different genes in progressive deterioration showed that ACE DD allele increased the odds of progressive deterioration by 14 times. Peruzzi et al on the

contrary found higher incidence of II genotype in cases [30].

AGT gene: Lovati et al found involvement of AGT CC gene polymorphism in ESRD patients in their study [43]. We also found its role while analysing the sub group of progressive deteriorators but not while comparing the CAKUT and non CAKUT population overall.

While analysing the renal function variables, we found that children with PUV had the least GFR as compared to PUJO and VUR population. Progressive deterioration was seen in significant proportion i.e. 20% of children with CAKUT. It was more common in children with PUV.

While assessing the cumulative effect of pathogenic alleles of different RAS genes, co-existence of DD allele with other alleles had the most serious outcomes. Thus, there is fair possibility that DD allele of ACE is working like a second hit to increase the pace of deterioration in renal functions.

Limitations: Longer follow up period could have revealed more accurate temporal trends of progressive deterioration. It would have also helped in showing effects of surgical interventions. Parental studies could have shed light on penetrance and inheritance which is the essential information needed for genetic counselling. Despite a good sample size, 4 single nucleotide polymorphisms fell short of predicting whole of genetic risk factors. Wider genome analysis would become possible with advanced gene sequencing technologies giving a wholesome assessment of genetic etiology.

Pathogenesis of CAKUT is multifactorial so risk prediction studies need to be done to assess the individual contribution of genetic, anatomic, and biochemical factors. Gene polymorphism studies will help in better risk stratification and thus will lay the foundation of genetic counselling in future. To conclude, CAKUT is a very intricate spectrum of anomalies and needs multi pronged approach for monitoring- genetic studies, serial imaging and biochemical analysis. Preventing CAKUT may not be achievable presently but preventing the progression is definitely possible if we identify the high risk groups and renal damage at an early stage.

Statements and Declarations

Conflicts of interest

The authors declares that they do not have conflict of interest.

Funding

No funding was received for conducting this study

References

1. Ichikawa I, Kuwayama F, Pope IV JC, Stephens FD, Miyazaki Y. Paradigm shift from classic anatomic theories to contemporary cell biological views of CAKUT. Kidney international. 2002 Mar 1;61(3):889-98.
2. Sanna-Cherchi S, Ravani P, Corbani V, Parodi S, Haupt R, Piaggio G, Degli Innocenti ML, Somenzi D, Trivelli A, Caridi G, Izzi C. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. Kidney international. 2009 Sep 1;76(5):528-33.
3. Daneman A, Alton DJ. Radiographic manifestations of renal anomalies. Radiologic Clinics of North America. 1991 Mar;29(2):351-63
4. Nakanishi K, Yoshikawa N. Genetic disorders of human congenital anomalies of the kidney and urinary tract (CAKUT). Pediatrics International. 2003 Oct;45(5):610-6.
5. Atkinson MA, Ng DK, Warady BA, Furth SL, Flynn JT. The CKiD study: overview and summary of findings related to kidney disease progression. Pediatric Nephrology. 2021 Mar;36(3):527-38.
6. "ESPN/ERA-EDTA Registry UK Renal Registry," annual report, 2008, http://www.espn-reg.org/ .
7. Groothoff JW. Long-term outcomes of children with end-stage renal disease. Pediatric Nephrology. 2005 Jul 1;20(7):849-53.
8. Krediet RT, Balafa O. Cardiovascular risk in the peritoneal dialysis patient. Nature Reviews Nephrology. 2010 Aug;6(8):451.
9. Renkema KY, Winyard PJ, Skovorodkin IN, Levtchenko E, Hindryckx A, Jeanpierre C, Weber S, Salomon R, Antignac C, Vainio S, Schedl A. Novel perspectives for investigating congenital anomalies of the kidney and urinary tract (CAKUT). Nephrology Dialysis Transplantation. 2011 Dec 1;26(12):3843-51.
10. Bajpai M, Chaturvedi PK, Bal CS, Sharma MC, Kalaivani M. Posterior urethral valves: Persistent renin angiotensin system activation after valve ablation and role of pre-emptive therapy with angiotensin converting enzyme-inhibitors on renal recovery. Journal of Indian Association of Pediatric Surgeons.

2013 Apr;18(2):74.
11. Bajpai M, Singh A. Plasma renin activity: An early marker of progressive renal disease in posterior urethral valves. Journal of Indian Association of Pediatric Surgeons. 2013 Oct;18(4):143.
12. Sinha A, Bajpai M, Panda S, Ranjan S, Sharma MC. Unilateral ureteric obstruction: Role of renin angiotensin system blockade on renal recovery: An experimental study. Journal of Indian Association of Pediatric Surgeons. 2012 Apr;17(2):49.
13. Bajpai M, Pratap A, Tripathi M, Bal CS. Posterior urethral valves: Preliminary observations on the significance of plasma Renin activity as a prognostic marker. The Journal of urology. 2005 Feb;173(2):592-4.
14. Panda SS, Bajpai M, Sinha A, Mallick S, Sharma MC. Effect of ipsilateral ureteric obstruction on contralateral kidney and role of renin angiotensin system blockade on renal recovery in experimentally induced unilateral ureteric obstruction. Journal of Indian Association of Pediatric Surgeons. 2013 Apr;18(2):58.
15. Bajpai M, Bal CS, Tripathi M, Kalaivani M, Gupta AK. Prenatally diagnosed unilateral hydronephrosis: Prognostic significance of plasma renin activity. The Journal of urology. 2007 Dec 1;178(6):2580-4.
16. Verma A, Panda SS, Bajpai M. Role of endoscopic treatment of vesico-ureteric reflux in downgrading renin angiotensin system activation. Journal of Pediatric Urology. 2014 Apr 1;10(2):386-90.
17. Bajpai M, Bal CS, Kumar R, Chaturvedi PK, Kalaivani M, Gupta AK. Persistent renin-angiotensin system activation after anti-reflux surgery and its management. Journal of Pediatric Urology. 2011 Dec 1;7(6):616-22.
18. Bajpai M, Pal K, Bal CS, Gupta AK, Pandey RM. Role of plasma renin activity in the management of primary vesicoureteric reflux: A preliminary report. Kidney international. 2003 Nov 1;64(5):1643-7.
19. Bajpai M, Pratap A, Somitesh C, Tyagi J. Angiotensin converting enzyme gene polymorphism in Asian Indian children with congenital uropathies. The Journal of urology. 2004 Feb;171(2):838-40.
20. Bajpai M, Puri A, Tripathi M, Maini A. Prognostic significance of captopril renography for managing congenital unilateral hydronephrosis. The Journal of urology. 2002 Nov;168(5):2158-61.
21. Anand S, Bajpai M, Khanna T, Kumar A. Influence of genetic polymorphism in renin-angiotensin system-candidate genes on urinary trefoil family factor 3 levels in children with congenital anomalies of kidney and urinary tract. Pediatric Nephrology. 2021 Jul 19:1-7.
22. Vivante A, Kohl S, Hwang DY, Dworschak GC, Hildebrandt F. Single-gene causes of congenital anomalies of the kidney and urinary tract (CAKUT) in humans. Pediatric nephrology. 2014 Apr 1;29(4):695-704
23. In Docimo, S. G., In Canning, D., In Khoury, A., & In Salle, J. L. P. (2018). *The Kelalis--King--Belman Textbook of Clinical Pediatric Urology, Sixth edition*
24. Yosypiv IV. Congenital anomalies of the kidney and urinary tract: a genetic disorder?. International Journal of Nephrology. 2012 Jan 1;2012.
25. Chen F. Genetic and developmental basis for urinary tract obstruction. Pediatric nephrology. 2009 Sep 1;24(9):1621-32.
26. Weber S. Novel genetic aspects of congenital anomalies of kidney and urinary tract. Current opinion in pediatrics. 2012 Apr 1;24(2):212-8.
27. Song R, Yosypiv IV. Genetics of congenital anomalies of the kidney and urinary tract. Pediatric Nephrology. 2011 Mar 1;26(3):353-64. Yosypiv IV. Renin–angiotensin system–growth factor cross-talk: a novel mechanism for ureteric bud morphogenesis. Pediatric Nephrology. 2009 Jun 1;24(6):1113-20.
28. Schaefer C. Angiotensin II-receptor-antagonists: further evidence of fetotoxicity but not teratogenicity. Birth Defects Research Part A: Clinical and Molecular Teratology. 2003 Aug;67(8):591-4.
29. Tabacova S, Little R, Tsong Y, Vega A, Kimmel CA. Adverse pregnancy outcomes associated with maternal enalapril antihypertensive treatment. Pharmaco epidemiology and drug safety. 2003 Dec;12(8):633-46.
30. Peruzzi L, Lombardo F, Amore A, Merlini E, Restagno G, Silvestro L, Papalia T, Coppo R. Low renin-angiotensin system activity gene polymorphism and dysplasia associated with posterior urethral valves. The Journal of urology. 2005 Aug;174(2):713-7. Lovati E, Richard A, Frey BM, Frey FJ, Ferrari P. Genetic polymorphisms of the renin-angiotensin-aldosterone system in

end-stage renal disease. Kidney international. 2001 Jul 1;60(1):46-54.
31. Kelly TN, Raj D, Rahman M, Kretzler M, Kallem RR, Ricardo AC, Rosas SE, Tao K, Xie D, Hamm LL, He J. The role of renin–angiotensin–aldosterone system genes in the progression of chronic kidney disease: findings from the Chronic Renal Insufficiency Cohort (CRIC) study. Nephrology Dialysis Transplantation. 2015 Oct 1;30(10):1711-8.
32. Gribouval O, Gonzales M, Neuhaus T, Aziza J, Bieth E, Laurent N, Bouton JM, Feuillet F, Makni S, Amar HB, Laube G. Mutations in genes in the renin-angiotensin system are associated with autosomal recessive renal tubular dysgenesis. Nature genetics. 2005 Sep;37(9):964-8.
33. Hahn H, Ku SE, Kim KS, Park YS, Yoon CH, Cheong HI. Implication of genetic variations in congenital obstructive nephropathy. Pediatric nephrology. 2005 Nov 1;20(11):1541-4.
34. Rigoli L, Chimenz R, Di Bella C, Cavallaro E, Caruso R, Briuglia S, Fede C, Salpietro CD. Angiotensin-converting enzyme and angiotensin type 2 receptor gene genotype distributions in Italian children with congenital uropathies. Pediatric research. 2004 Dec;56(6):988-93.
35. Stanković A, Živković M, Kostić M, Atanacković J, Krstić Z, Alavantić D. Expression profiling of the AT2R mRNA in affected tissue from children with CAKUT. Clinical biochemistry. 2010 Jan 1;43(1-2):71-5.
36. Cordell HJ, Darlay R, Charoen P, Stewart A, Gullett AM, Lambert HJ, Malcolm S, Feather SA, Goodship TH, Woolf AS, Kenda RB. Whole-genome linkage and association scan in primary, nonsyndromic vesicoureteric reflux. Journal of the American Society of Nephrology. 2010 Jan 1;21(1):113-23.
37. Nishimura H, Yerkes E, Hohenfellner K, Miyazaki Y, Ma J, Hunley TE, Yoshida H, Ichiki T, Threadgill D, Phillips III JA, Hogan BM. Role of the angiotensin type 2 receptor gene in congenital anomalies of the kidney and urinary tract, CAKUT, of mice and men. Molecular cell. 1999 Jan 1;3(1):1-0
38. Coran, A. G., & Adzick, N. S. (2012). Pediatric surgery. Philadelphia, PA: Elsevier Mosby
39. Narasimhan KL, Madhu K, Balpinder K, Monica A, Kumar MJ, Rai MB, Anish B, Bikash M. Association of angiotensin converting enzyme and angiotensin type 2 receptor gene polymorphisms with renal damage in posterior urethral valves. Journal of pediatric urology. 2010 Dec 1;6(6):560-6.
40. Hulyam K, Aysegul B, Veysi GH, Demet O, Irfan D, Ertugrul C, Didem CT, Banu B, Miris D. Frequency of angiotensin II type 1 receptor gene polymorphism in Turkish acute stroke patients. Journal of cellular and molecular medicine. 2013 Apr;17(4):475-81.
41. Nałogowska-Głośnicka K, Łacka B, Zychma MJ, Grzeszczak W, Zukowska-Szczechowska E, Poreba R, Michalski B, Kniazewski B, Rzempołuch J, PIH Study Group. Angiotensin II type 1 receptor gene A1166C polymorphism is associated with the increased risk of pregnancy-induced hypertension. Med Sci Monit. 2000 May 1;6(3):523-9.
42. Akbar SA, Khawaja NP, Brown PR, Tayyeb R, Bamfo J, Nicolaides KH. Angiotensin II type 1 and 2 receptors gene polymorphisms in pre-eclampsia and normal pregnancy in three different populations. Acta obstetricia et gynecologica Scandinavica. 2009 Jan 1;88(5):606-11.
43. Lovati E, Richard A, Frey BM, Frey FJ, Ferrari P. Genetic polymorphisms of the renin-angiotensin-aldosterone system in end-stage renal disease. Kidney international. 2001 Jul 1;60(1):46-54.

National Board of Examination - Journal of Medical Sciences

Volume 1, Issue 3, Pages 135–142, March 2023

DOI 10.61770/NBEJMS.2023.v01.i03.003

REVIEW ARTICLE

75 Years of Vaccination in India and Way Ahead

Anshita Mishra*, Gurmeet Singh, Aashish Yadav, Babul Kumar and Pragya Sharma

Department of Community Medicine, Maulana Azad Medical College, New Delhi, India 110002

Accepted: 12-February-2023 / Published Online: 01-March-2023

Abstract

Prevention of diseases through vaccination has been a key component of Preventive Medicine. The history of vaccination in India begins from pre-Independence where Small pox vaccine was introduced for the first time and administered through tikadars(vaccinators) till post-Independence where the political will and the medical experts helped us eliminate Poliomyelitis- a dreaded disease. Post-Independence, India has come a long way from starting the manufacturing of vaccines, introducing Expanded Polio Immunization (1978) and Universal Immunization Programme (1985) to a path breaking performance in Covid-19 vaccination. The Covid-19 vaccination has brought India under the limelight globally and are ready to take up further challenges. The Covid-19 vaccination is a model in itself for the world and has been analysed in detail from planning to its execution. This paper attempts to review the history of vaccination from pre-Independence era in brief to a greater focus on how it paved a way for further developments in the domain of Vaccination post-Independence in the country.

Keywords: vaccination, covid-19 vaccination, India, expanded programme on immunization, universal immunization programme

*Corresponding author: Anshita Mishra
Email: amishra371@gmail.com

Introduction

The description of infectious diseases like Tuberculosis, leprosy, etc. in our ancient literatures tells us that they have been present in our society since times immemorial. Alongside human evolution and development, man has tried to treat these diseases, moreover, eliminate these diseases from the Society. Man has been curious to study about these diseases and has been working continuously to remove them since health has always been considered a human right. While treating a disease has been an integral part of this system, so has been the idea of prevention. Prevention has been considered the ultimate goal of our system where everybody can lead a healthy life. As Public Health Specialists, our main area of concern is prevention of diseases. To implement this, vaccination has been considered a major pathway towards achieving this goal. The history of usage of vaccines dates back to 1000 AD in China in preventing smallpox disease [1]. The concept of vaccination reached India in early 1800s after the arrival of smallpox vaccine as the disease was well prevalent in India, such that it was also called Indian plague [1]. Starting from having paid vaccinators to the Compulsory Vaccination Act which came into practice in 1938 and moved towards our goal of maximum immunization coverage but still a lot was lacking at the policy level. Not only through transportation but in late 1800s, we also developed the Cholera vaccine, but the immunization failed as there were many deaths reported post cholera vaccination [1].

Although, in the later years, the cause of death was found and reported to be due to programmatic errors only [1]. Even when being ruled by the British, various vaccination laboratories were being set up in India. While on one side, we were keen on being self-capable in manufacturing of vaccines locally and making India a self-reliant nation, our concern also shifted towards the resistance among the citizens towards vaccinations. After a lot of research, it was found that one of the major causes of this resistance was the side effects after vaccination, which otherwise is a usual phenomenon but kept the concept of Immunization in bad light as it was not being dealt appropriately. To rectify this, the concept of reporting of Adverse Events Following Immunization (AEFI) came up and was perceived as one of the strengthening tools towards immunization coverage [2,3,4]. This way the seeds of Immunization were sown in the country. Previous literature has described the fight against various diseases through vaccination under disease headings both pre- and post- Independence. Through this review, we present a comprehensive overview on the vaccination history from pre-Independence to post Independence and how the country's journey vaccination programme during the COVID-19 pandemic has brought India under the global limelight for the first time.

Literature Review

1. Fight against Polio

Nearing India's Independence, Polio had created an aftermath in the country. After various scientists failed at their discoveries, it was Jonas Salk who developed the trivalent vaccine in 1955. Further, Sabin developed an oral polio vaccine (OPV) and trials were done by 1960. Concurrently, Vaccine associated paralytic poliomyelitis (VAPP) was found to be associated more with OPV than the Sabin variant in 1962. But OPV outnumbered IPV through various research and proved more beneficial and efficient for mass use in 1964 and it was implemented in every country by WHO through Expanded Program on Immunization (EPI) in 1974. It was only in 1970 that the indigenous OPV production started in India. In 1988 when the Global Polio Eradication Initiative (GPEI) was being launched, the OPV was chosen for use in all these countries and the program received the due attention because of World Health Assembly's target to eradicate polio by 2000 [5].Table 1 shows the timeline progress in achieving the polio free status of India [6,7,8].

Table 1. Timeline of polio eradication

S.No	Year	Milestone achieved
1.	1988	World Health Assembly set a target of polio eradication by 2000.
2.	1995-96	First two National Immunization Days for polio vaccination conducted.
3.	1996	Vaccine Vial Monitor used on polio vaccine vials.
4.	1999	Polio drive moved from booth activity to house-to-house coverage.
5.	2005	Monovalent oral polio vaccine was used.
6.	2010	Bivalent oral polio vaccine used for polio campaigns in India.
		Last reported wild polio virus in sewage sample from Mumbai, India.
		Last case of wild polio virus type 3 reported from Pakur, Jharkhand.
7.	2011	Last case of any type of wild polio virus reported from Howrah, West Bengal.
8.	2012	WHO removes India from the list of polio endemic countries.

During the next six years, extensive efforts were made particularly in states of Tamil Nadu, Kerala and Delhi following which two National Immunization Days (NIDs) were conducted. By 1996, Vaccine vial monitors also came into use in our country to further enhance the efficacy of the vaccine and its monitoring. The programme conceived its full form in 1997 when WHO and India began the National Polio Surveillance Project. As a result, within only two years of inception, the last case of Polio (WPV-2) was reported in 1999. Gaining further momentum, the strategy of booth vaccination was further expanded to door-to-door coverage of the whole target population. In 2005, monovalent OPV had come into use but in 2010, bivalent OPV was used in these campaigns. We could successfully report the last sample of polio virus in 2010 in sewage sample in Mumbai. The last case of any type of WPV was reported in Howrah, West Bengal on 13th of January 2011. Following that, India received a Polio free status from WHO. The success of this program has been acknowledged by WHO and our country has been appreciated by them quoting "*The strategies for polio eradication work when they are fully implemented. This is clearly demonstrated by India's success in stopping polio in January 2011, in arguably the most technically challenging place, and polio-free certification of the entire WHO Southeast Asia Region in March 2014*" [7,8].

2. Fight against Tuberculosis and Small pox

After the Independence in 1947, focus was brought onto Preventive health and so to the Vaccination program of the country. The logistical concerns were addressed, and various manufacturing units were set up in the country. BCG vaccine laboratory was set up in 1948 and by 1951; liquid BCG vaccine was made available for mass campaigns. The BCG vaccination gave an immediate boost to the vaccination program of the country where it was inculcated in National Tuberculosis Control Programme started in 1962. This happened as Tuberculosis was taking a shape of an epidemic in the country. After various deliberations in relation to the efficacy of the BCG vaccine, it was realized to be given at an early age i.e., within first year of birth and was included in the UIP. All these amendments were possible only because of the research trials done by our indigenous Institutes and the importance of self-reliance was understood [9].

Not only this, World Health Assembly's resolution to eradicate smallpox in 1958 was also taken up leading to genesis of National Smallpox Eradication programme in 1962 with an objective of vaccinating the entire population in the following three years. By 1965, live attenuated freeze-dried smallpox vaccine was also made available for larger population [9].

Two years later, freeze dried BCG and OPV became available in India as well. But

the results were disappointing because the disease outbreak could still not be reduced due to lack of access to the target population. In 1967-1968, the smallpox eradication strategy was reformulated in terms of surveillance along with epidemiological investigation of outbreaks and rapid containment drives. Even the vaccination technique from using a rotary lancet was changed to bifurcated needle technique in 1969. The old liquid vaccine was replaced by more potent, heat-stable and freeze-dried vaccine in 1971.By mid-1973, the vaccination helped to contain the disease in select States of India. An intensified approach was undertaken, and a phase wise implementation of the program was done where firstly the disease was searched and attempts were made for containment. In the second phase, UP, Bihar, Madhya Pradesh and West Bengal were targeted where each village and every house was screened to detect any suspected case within a one-week period. Case investigations and containment operations were done in the next three weeks. Still, the count remained at 188,000 cases and 31,000 deaths. The Government intensified the search, containment process and the vaccination efforts. With continued surveillance, the last reported case came in 1975 and India received the Smallpox free status in 1977. The journey of India becoming "Smallpox free" is a great learning tool in the history of India as to how a socio-political approach with strong determination can help reach great heights [9,11,12].

3. Fight against Vitamin A deficiency & Expanded Programme on Immunization (EPI)

The National Prophylaxis Programme against Nutritional Blindness due to Vitamin A Deficiency (NPPNB due to VAD) was developed in 1970 for preventing nutritional blindness due to keratomalacia. Being a completely centrally sponsored programme, it was launched in a phasic manner as an urgent remedy to combat xerophthalmic blindness. This Programme was initiated in 11 States of the country. After achieving positive results during Evaluation conducted by the National Institute of Nutrition (NIN), Hyderabad in 1976 in two States, the Programme was extended to all States in the country. In view of operational feasibility, the administration of first dose of Vitamin A was linked to measles immunization. Presently, Vitamin A Supplementation (VAS) is being implemented through the existing network of Primary Health Centres and Sub-Centres. The services of Integrated Child Development Services [ICDS] functionaries are being utilized for the implementation of the Programme [13,14].

In 1974, Expanded Programme on Immunization was developed and was launched in 1977 globally with the aim to immunize every child against diphtheria, pertussis, tetanus, poliomyelitis, typhoid and tuberculosis by 1990.In 1974, below 5% children were receiving a 3rd dose of DPT and poliomyelitis vaccines within their 1st year of life. These coverage levels have now exceeded beyond 50% and millions of cases of the target disease have been successfully prevented. The next decade came to be a boon for the Vaccination program of the country where various milestones were achieved from indigenous measles vaccine production, manufacturing of IPV in 1984 by setting up various public- private joint venture companies like Indian Immunological Limited, Panacea Biotech, Indian Vaccine Company Limited (IVCOL), Bharat Immunological and Biological Limited (BIBCOL) [9].

The world looked at India at a fast-moving pace in becoming self-dependent, adopting excellent approaches for Vaccine Preventable Diseases (VPDs). In 1985, EPI was renamed to Universal Immunization Programme (UIP) where typhoid vaccination was replaced by measles vaccine and more focus was made to those less than one year in the programme. The focus was now extended to six basic vaccines to infants and tetanus vaccine to pregnant women. During this period, India started manufacturing of many new vaccines which became licensed and

available in the market. There have been additional national efforts to improve coverage, which include launch of Immunization Strengthening Project, Urban Measles Campaign and Border Districts Cluster Strategy, etc. After another revision of AEFI guidelines in 2005-2006 improved the reporting system and is further being revised continuously [15].

India released its first National Vaccine Policy in 2011 which envisages the guiding principles for functioning of immunization programme in the country. Following this, 2012-13 was declared as "Year of intensification of Routine Immunization". Focus was now paid to 239 poor performing districts of India with the intent to prioritize conduction of immunization weeks along with improving cold chain status and for better coverage [16].

4. India's journey on becoming self-reliant

Another boost to the manufacturing of vaccines in the country happened in 2009 when three manufacturers developed pandemic flu vaccine in a short period of time. Following this, a new bivalent oral cholera vaccine, a meningitis-A vaccine and an indigenous Japanese Encephalitis vaccine were developed by Indian manufacturers in collaboration with international partner and are now licensed in India. An indigenous Rota virus vaccine ROTAVAC was also announced in 2013 and its successful trial was considered an important milestone and a perfect example of successful public-private partnership [17].

5. Immunization coverage

Figure 1 shows the percentage of children who received all basic vaccinations [BCG, MCV/ Measles/ MR/ MMR, and three doses each of DPT/Penta and polio vaccine] increased from 62.0% in NFHS-IV (2015-16) to 76.7% in NFHS-V (2019-20) report. As per NFHS-5 report, over four-fifths of children received complete three doses of hepatitis B vaccine. 95% children received BCG vaccine, highest amongst all [18].

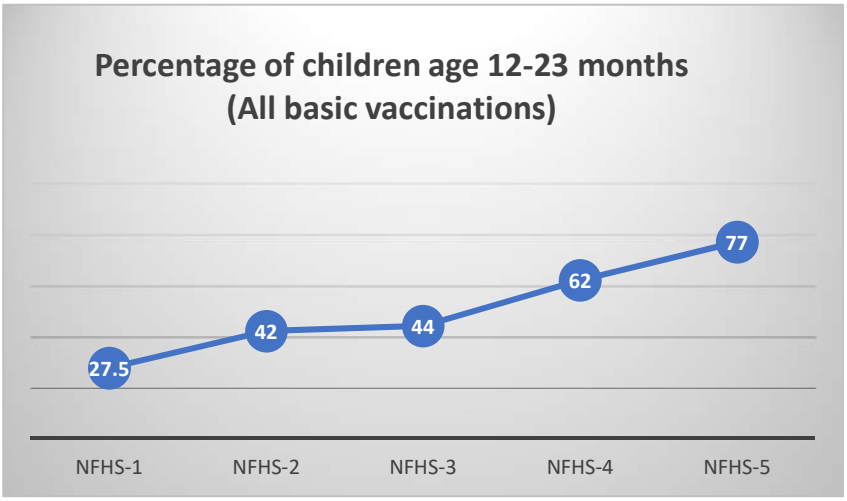


Figure 1. Percentage of children age 12-23 months (all basic vaccinations)

During the "Year of intensification of routine immunization" various strategic actions were initiated towards increased funding for supportive supervision and mobilization of beneficiaries. A web-based mother and child tracking system (MCTS) with the objective of preventing left out and drop-outs was also introduced. Towards strengthening of Adverse Event Following Immunization (AEF)] surveillance, activities including establishing a national AEFI Secretariat, collaboration with medical

colleges for research assistance, revision of the guidelines and capacity building across the country were taken up. The National cold chain management information system (NCCMIS) was also further established to ensure vaccine safety and effective cold chain management. In 2014, Mission Indradhanush was launched as a strategic endeavour by the Ministry of Health & Family Welfare (MoHFW), Government of India to expand the immunization coverage to at least 90% over the next five years. The country was categorized into high, medium and low focus districts, thereby Phase I of Mission Indradhanush targeted 201 high-focus districts of the country. Phase II targeted 352 districts between October 2015 and January 2016. During these two phases of Mission Indradhanush more than 3.7 million children were fully immunized [19].

The basic strategy included ensuring availability of sufficient vaccinators through revision of micro plans in all areas including slums, construction sites, and other hard to reach areas, achieving better community participation by intensive communication, special focus on capacity building through intensive training of the workers and ensuring engagement and accountability of administrative machinery for better implementation.

In spite of all positive changes, we still face several challenges in the form of incomplete coverage because of population resistance at certain levels, weak AEFI surveillance and reporting system along with problems at the funding level for conducting operational research, trials and self-sufficiency at manufacturing level. But today, beyond the aftermath of COVID-19 and the brilliant work done by the country in discovery, manufacturing and administration of COVID-19 vaccine has brought India at the top of the globe where we stand as an example of how a strong determination and a good cooperation of the socio-political leaders with the medical fraternity can work wonders for the masses.

6. Vaccination during COVID-19 pandemic

After the COVID-19 pandemic hit us, the urgent need of vaccine was realized at international level. India is amongst the first few countries to have developed and manufactured the COVID-19 vaccines: Covi-shield, the recombinant ChAdOx1 nCoV- 19 Corona Virus Vaccine, COVAXIN and SPUTNIK-V. With the belief in Vasudhaiva Kutumbakam (World as one family), Government of India supplied 66.37 million doses of COVID-19 vaccines to 95 countries. Recently, the National Regulator also granted permission for restricted use in emergency like situations to ZyCoV-D, the World's first DNA based COVID-19 vaccine [20]. Alongside, the following vaccines are also in advanced stages of clinical trials: sub-unit vaccine (Corbevax), mRNA vaccine (HGCO19) and Intra-nasal vaccine.

Not only the manufacturing part, but the inculcation of the technology through Co-Win portal helped the programme managers in registration and tracking of each beneficiary of COVID-19 vaccination and every vaccination event along with real time information of vaccine stocks, vaccination process, digital certification, etc. This is also serving as a platform for registration and scheduling of vaccination appointments making the system all the more effective thereby promoting easy visualization, hassle free registration and maintaining transparency in the system.

A Co-WIN Global Conclave was jointly organized in July 2021 by MoHFW, Ministry of External Affairs (MEA) and National Health Authority (NHA) with the objective to extend the platform as a digital public good to the world where more than hundred countries have shown interest for uptake and operationalization of Co-WIN. A comprehensive strategy based on six key principles was evolved including adoption of a Universal Programme approach along with provision of "free of cost" vaccines, "Aatma-nirbharta"(self-reliance) for which the Government provided support to develop indigenous vaccines, adoption of "layered

approach" included vaccinating Frontline Workers, followed by vulnerable population and ultimately for all over 18 years of age, development of Co-Win portal to facilitate the process of mass vaccination, "One Earth, One Health" approach with proactive sharing of our experiences, expertise and resources with the global community and engagement of all key stakeholders.

The National COVID-19 vaccination drive of India is world's largest vaccination drive and has been unprecedented in both scale and reach. India's well visioned vaccine production and administration effort as recommended by National Expert Group on Vaccine Administration for COVID-19 (NEGVAC) is based on four key points including strong IT framework through Co-Win portal, facilitating indigenous research along with development and production, mobilizing supplies from all sources and adherence to COVID-19 appropriate behaviour.

Vaccination drive has been monitored at various stages by the National, State and District Task Force, as per the monitoring mechanism defined in operational guidelines of COVID-19 vaccination drive. The main emphasis is over vaccination coverage status; AEFI reported and vaccine wastage, availability and utilization, supply chain issues, policy decisions regarding COVID vaccination drive etc. The AEFI surveillance system under UIP has been strengthened for COVID-19 AEFI management and reporting by inclusion of Super-specialists as well, revision in contents of Anaphylaxis kits, training of vaccinators on usage of Anaphylaxis kit, etc. To enhance the reporting, minor, severe and serious AEFIs which occur after COVID-19 vaccinations can be reported by vaccinators and district immunization officers directly on the Co-WIN app. In addition to entering of the AEFI related data, relevant investigation forms and hospital records, etc. can also be uploaded on the application [20].

Conclusion

The whole process of strengthening of vaccination in our country is far more elaborate than discussed in this small segment where every event has a detailed background with merits and a history of failures. But we need to review the history from time to time as a part of learning on what to do and what not to do. And today, as we celebrate "Azadi ka Amrit Mahotsav"(75 years of Independence) it is for sure that India has proved its mettle and stood out on a global platform.

Statements and Declarations

Competing interests: Not Applicable

Conflict of interest: Not Applicable

References

1. Bennett M. Passage through India: global vaccination and British India, 1800-05. Journal of Imperial and Commonwealth History. 2007; 1: 201-20.
2. Riedel S. Edward Jenner and the history of smallpox and vaccination. Baylor University Medical Center Proceedings. 2005; 18(1): 21-25.
3. Basu RN. Smallpox eradication: lessons learnt from a success story. Natl Med J India. 2006; 19(1):33-6.
4. Bazin H. Vaccination: a history from Lady Montagu to genetic engineering. John Libbey Eurotext; 2011.
5. Grassly NC, Fraser C, Wenger J, et al. New strategies for the elimination of polio from India. Science. 2006; 314 (5802): 1150-3.
6. The National Polio Surveillance Project. A Government of India- WHO Collaboration. www.npspindia.org,
7. John TJ, Vashishtha VM. Eradicating poliomyelitis: India's journey from hyperendemic to polio-free status. The

Indian Journal of Medical Research. 2013; 137(5): 881.
8. Vashishtha VM, Kamath S: A Brief History of Vaccines Against Polio. Indian pediatrics. 2016; 7:53.
9. Lahariya C: A brief history of vaccines & vaccination in India. The. Indian Journal of Medical Research. 2014; 139:491.
10. Strassburg MA: The global eradication of smallpox. Am J Infect Control. 1982; 10(2):53-9. DOI 10.1016/0196-6553(82)90003-7.
11. Luca S, Mihaescu T: History of BCG Vaccine. MAEDICA – a Journal of Clinical Medicine. 2013; 8(1): 53-8.
12. Trial TP: Trial of BCG vaccines in south India for tuberculosis prevention: first report. Bull World Health Organ.. Indian J Tuberc. 1979; 57(5): 819-27.
13. Kapil U, Sachdev HP: Massive dose vitamin A programme in India--need for a targeted approach. Indian J Med Res. 2013; 138(3): 411-17.
14. Kapil U, Chaturvedi S, Nayar D. National nutrition supplementation programmes. Indian Pediatr.1992; 29(12):1601-13.
15. Malik A, Haldar P, Ray A, Shet A, Kapuria B, Bhadana S, Santosham M, Ghosh RS, Steinglass R, Kumar R. Introducing rotavirus vaccine in the Universal Immunization Programme in India: From evidence to policy to implementation. Vaccine. 2019 Sep 16; 37(39): 5817-24.
16. Vashishtha VM. Status of immunization and need for intensification of routine immunization in India. Indian pediatrics. 2012; 49(5): 357-61.
17. Bhandari N, Rongsen-Chandola T, Bavdekar A, et al.Efficacy of a monovalent human-bovine [116E] rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2014; 383(9935): 2136-43. DOI: 10.1016/S0140-6736(13)62630-6
18. NFHS - 5 Fact Sheets for Key Indicators.
19. Immunization Handbook for Medical Officers Reprint 2017. Ministry of Health and Family Welfare, India. New Delhi: 2017.
20. The World's Largest Vaccination Drive Booklet. Ministry of Health and Family Welfare, India. https://www.mohfw.gov.in/TheWorld%27sLargestVaccinationDriveBooklet/.

National Board of Examination - Journal of Medical Sciences

Volume 1, Issue 3, Pages 143–150, March 2023

DOI 10.61770/NBEJMS.2023.v01.i03.004

REVIEW ARTICLE

Observational Study of Outcome of Open Hemorrhoidectomy (Miligan Morgan's Technique) vs. Transanal Suture Hemorrhoidopexy (Chivate's Procedure)

Mohammed Motiwala*, Sandeep Kansal and Hardik Makwana

Department of General Surgery, Government Medical College, Surat, India

Accepted: 19-February-2023 / Published Online: 01-March-2023

Abstract

Background: The comparison of outcome of open hemorrhoidectomy vs transanal suture hemorrhoidopexy

Aims & Objectives: To evaluate and compare the outcome of open hemorrhoidectomy (Milligan Morgan`s technique) and transanal suture hemorrhoidopexy (Chivate`s procedure).

Methodology: Observational Retrospective and concurrent prospective cohort study utilizing 25 patients in two groups.

Results: Statistical Analysis suggest significant advantage of transanal suture hemorrhoidopexy over open hemorrhoidectomy.

Keywords: Hemorrhoides, open hemorrhoidectomy, suture hemorrhoidopexy, pain.

*Corresponding author: Mohammed Motiwala
Email: motiwalamohammed97@gmail.com

Introduction

Hemorrhoids, one of the most common pathology to be present at colorectal clinic among general population. Hemorrhoids are normal vascular cushions suspended in the submucosal layer of anal canal by longitudinal connective tissue and smooth muscle fibers [5]. Although hemorrhoids are normal structure, the term hemorrhoid (Hem-uh-rrhoids=swollen veins in your anus and lower rectum; similar to varicose veins) indicates a pathologic or symptomatic process [8].

Hemorrhoidal disease presents with the chief complains of more commonly bleeding, difficulty in defecation/constipation, prolong straining, soiling, and pruritus [2,3]. Constipation and Prolong Straining are widely believed to cause hemorrhoids because hard stool and increased intraabdominal pressure could cause obstruction of venous return, resulting in engorgement of hemorrhoidal plexus but recently diarrhea is also a risk factor for development of hemorrhoides [4].

To reduce constipation which is a main precipitating factor, is the main leading modification which relieves the complaints in many patients, if not all. This is done by dietary measures and bulk forming agents. Failure to the conservative life style modification measures will necessitate some form of operative intervention.

For years, hemorrhoidal excision was done which reduces the disease burden but it is associated with many complications and morbidity such as post-operative pain [6].

In 1998, Longo proposed the use of a specifically designed instrument, circular stapler for surgical treatment of grade III and IV hemorrhoids [7]. This surgery depends on shortening and fixing of prolapsed anal cushions to their original position above the dentate line, known as stapler hemorrhoidopexy. Modification of this technique using sutures was introduced by Dr Chivate which was termed as Transanal Suture Hemorrhoidopexy [19].

Our present study aims to provide evidence for the painless treatment for hemorrhoids and to compare and evaluate Open hemorrhoidectomy (Milligan Morgan`s technique) vs Transanal Suture hemorrhoidopexy (Chivate`s procedure) in providing effective procedure for hemorrhoids.

Methodology

As this study is retrospective with concurrent prospective observational study, purposive sampling with collection of case sheets and papers from record room with permission from Medical Superintendent to get access to the case papers which were noted in case paper of the patients who were operated for hemorrhoid surgeries at tertiary care hospital of South Gujarat. With the follow up, post operative complications were noted.

Inclusion Criteria

1. Patients who had undergone or will undergo operative intervention for 2nd degree, 3rd degree hemorrrhoids and 4th degree- prolapsed and edematous hemorrhoids
2. Patients 18-65 years

Exclusion Criteria

1. Patients <18 or >65 years.
2. Immuno-compromised/comorbid patients.
3. Death of patients in post operative period due to systemic cause

Outcome Parameters

To study immediate post operative complications i.e. Pain (According to Wong Bakers Faces-WBF scale), Bleeding on discharge, pain, bleeding, discharge, fecal incontinence, fever, stricture (basis on the follow up), operative duration, hospital stay in both the surgeries i.e. Milligan Morgan`s open Hemorrhoidectomy and Chivate`s Transanal Suture Hemorrhoidopexy (At 1 month, subsequent follow up and 6 month interval)- all the details documented in haemorrhoid (perianal) surgeries at tertiary care hospital of South Gujarat.

Technique [9,12]

This method uses the specific operative proctoscope (Fig. 1), which is made up of a plastic (pvc=poly vinyl chloride) tube of 3.6 cm inner and 3.8 cm outer diameters; along with dual use handle for light source connected to fiber optic and for holding [9]. The handle of fiber optic is opposite to the slit for working area in anal canal. The proximal end of the tube is conical and smooth that closes the tube, which facilitates the introduction of the proctoscope and prevents fecal matter to enter in the operation field. Multiple modifications of Chivate`s proctoscope available in form of length and material too. In our study we used the same above mentioned plastic material - that has economical sterilization method and more length calibration, so hemorrhoidopexy can be done easily as well. Over the inner aspect of the scope, there are multiple calibrated markings at 1 cm interval. The operating scope retracts the anus and rectum to provide optimum space without over stretching.

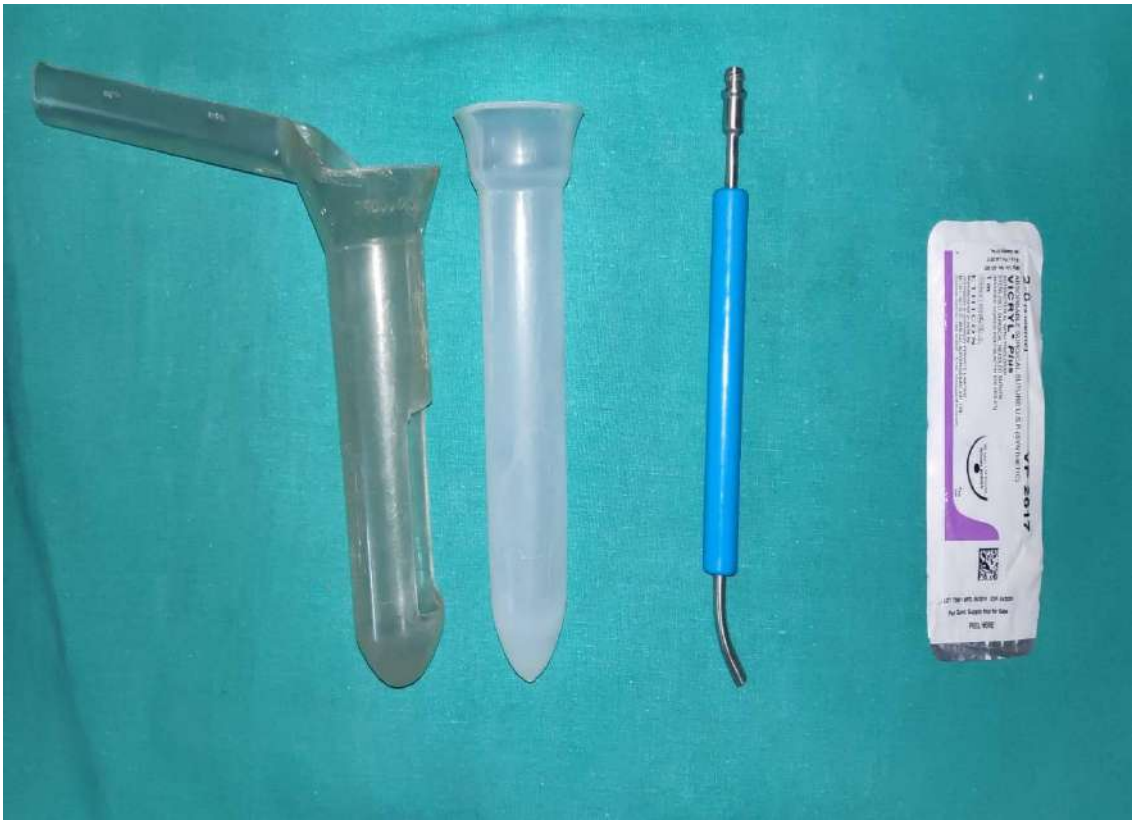


Fig. 1. Materials required for Chivate`s suture hemorrhoidopexy

We used metal malleable tongue depressor to depress the pile masses upwards. First anoscope is inserted and then anoscope along with operating proctoscope is inserted. Sliding anoscope is removed. Entire anal canal easily illuminated for the procedure. Using absorbable suture at 0.6-1 cm hemorrhoidopexy is performed.

The stitches are passed through the depth of the mucus-submucous and part of muscle, started at six o'clock position at a distance of 4 cm proximal to the dentate line. For the stitch a 2-0 polyglactin on round bodied 30 mm, 1 meter long ½ circle needle is used. Strict vigilance is required to prevent involvement of rectal wall. After the first knot, the next bite is started 1–2 mm next to the first knot, overlapping it 1-2 mm and is double locked, which is to avoid purse string effect. Circumferential suturing is done in similar manner. The last stitch is crossed over the first bite and then knotted. The second circumferential suture line is completed in a similar manner but above dentate line at 2 cm

distance. Due to visceral and autonomic nerve supply, little or no pain is perceived by the patient. (Fig. 2).

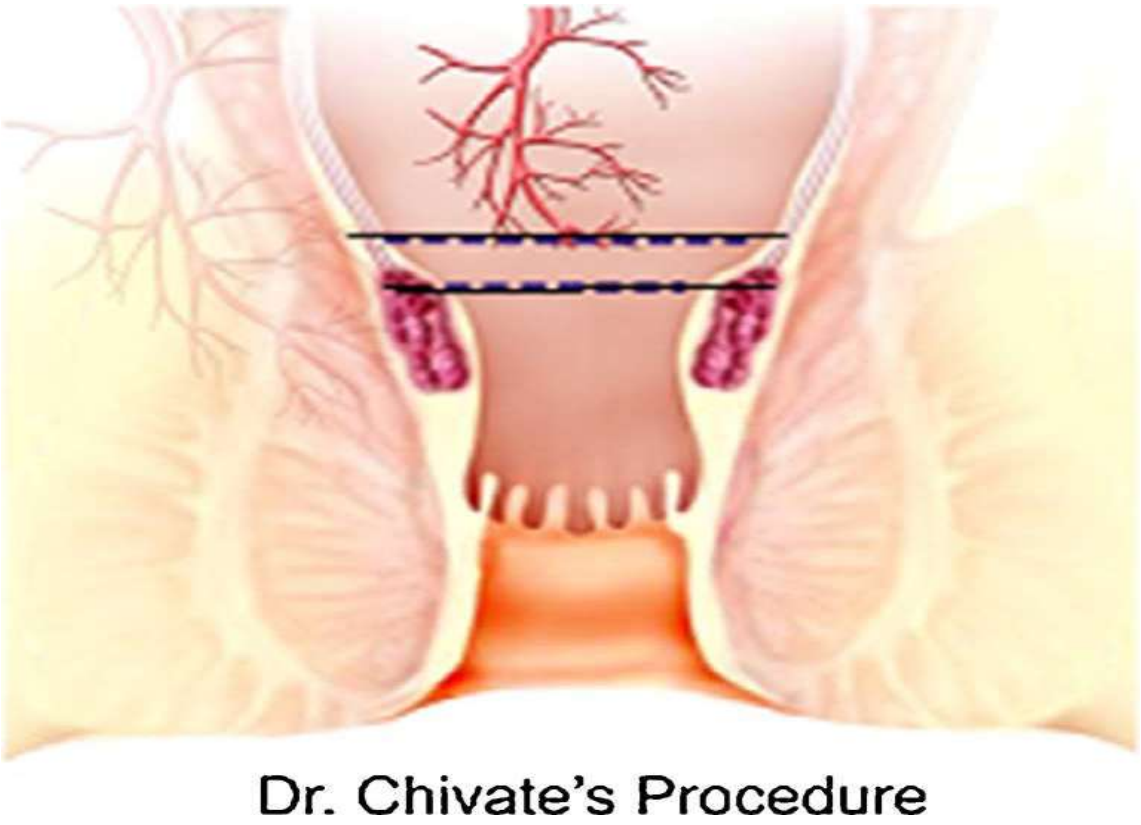


Fig. 2: Two cicumferential suture lines

Results

A sum of 50 patients for hemorrhoid surgery divided in equal groups in department of surgery, tertiary care hospital of South Gujarat were included in this study from July 2019 to August 2021. Statistical analysis was done using chi square test. For ease of description we use Group A as open hemorrhoidectomy (Milligan Morgan`s technique) and group B for transanal suture hemorrhoidopexy (Chivate`s Procedure) (Fig.4 & 5).

We observed that operative interval in 44% of group B took >35 mins in comparison to 20% in performing group A. P-value was 0.00086 stating that statistically it is significant.

For postoperative pain statistical analysis revealed that 12% incidence of postoperative pain that is >/=3 WBF pain score in group B and 68 % in group A(Fig.3) [11]. P value came out 0.00021 which is significant statistically. Statistics showed 12% incidence of postoperative bleeding in group B and 36 % in group A. P value came out 0.0473, suggestive of significant difference in both the groupsof significant difference in both the groups.

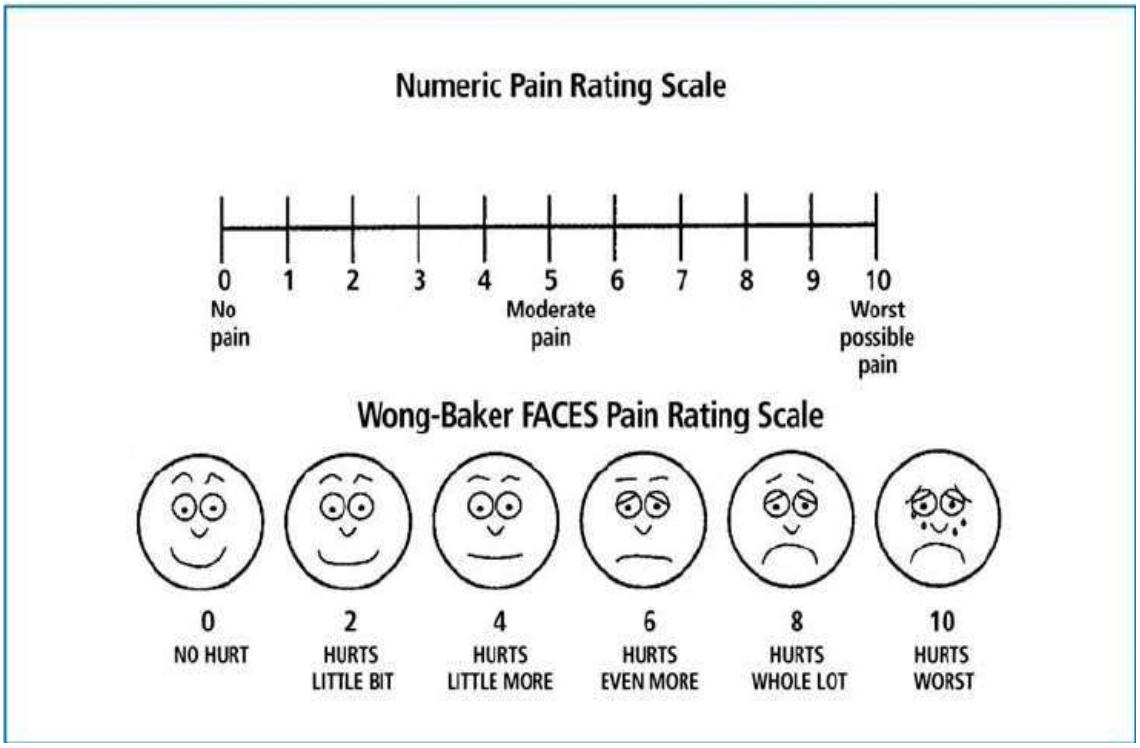


Fig. 3: WBF pain rating scale

On follow up assessment, pain persisted in 32% of patients and 28% had persistent bleeding in group A compared to 4% of patient had pain and bleeding in group B patients on 7th post operative day. From that, P value of 0.01034 and 0.0210 for pain and bleeding also signifies a difference in both the groups.

Many related local findings were noted at the follow up visit on day-7 of the patient which suggest that discharge was statistically not significant among both groups. Other findings by chi-square test revealed 16% incidence of fecal incontinence and 20% of patients developed anal stricture of group A. Whereas, group B had no such complain. Calculating P value came out for fecal incontinence and anal stricture were 0.037 and 0.01771 respectively, stating as significantly different.

Hospital in stay was studied and compared in the both the groups. Statistical analysis by chi-square test revealed 84% incidence of discharge <2 days and resumption of daily activities in group A and 24% in group A. P value of 0.035015 also suggested significant difference in the 2 groups statistically.

Recurrence at (follow up of) 28 days and on further visits (long term) ~6 month was studied and compared in both the groups. Statistical analysis using Chi-square test revealed that recurrence present in 4% in group B at each visit whereas in group A 20% and 25% at 2nd and 3rd visit respectively. P value came out to be 0.0823 and 0.009 respectively, which signifies the difference between 2 groups for the recurrence.

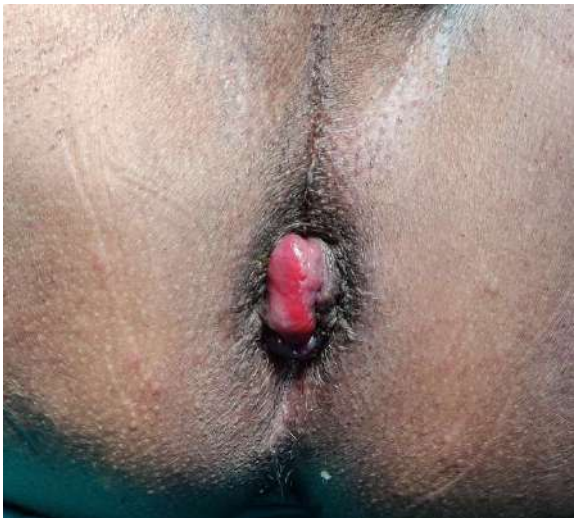


Fig. 4: Pre Operative

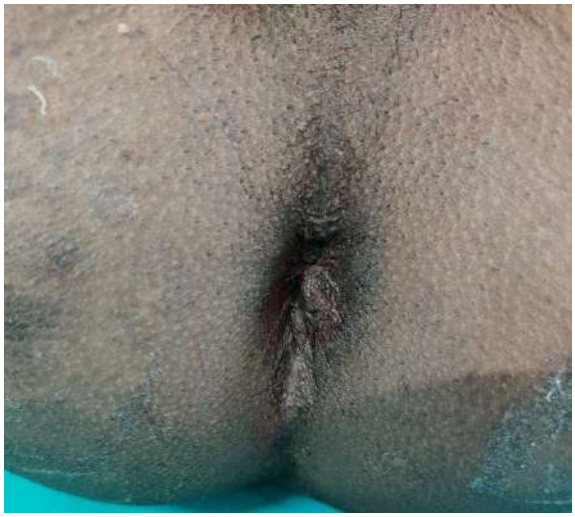


Fig. 5: Post Operative Day-7

Discussion

As we know, hemorrhoid is the persistent disease in the Indian subcontinent which needs to be treated to preserve daily life activity accordingly. According to the research which is extensively done in western regions recently such as LASER, Infrared coagulation which is not applicable widely on daily basis because of economical issues. Therefore, we considered studying conventional open hemorrhoidectomy (Milligan Morgan`s technique) and transanal suture hemorrhoidopexy (Chivate`s procedure), latter is again given by an Indian well renowned surgeon Dr. Chivate [9,10,12].

In our study, mean operative interval of surgery is 30 minutes in Group A and 35 minutes in Group B. This difference was statistically significant (P value 0.000086) which indicate that duration of time is more in hemorrhoidopexy. Open hemorrhoidectomy procedure requires less time for surgery. Mastakov et al found the similar result of mean operative interval of around 27.4 minutes for conventional open hemorrhoidectomy group on 27 patients [13]. Longer operative duration in suture hemorrhoidopexy patients can be attributable to the adaptation of surgeon to the new technique and longer learning curve for the new surgeon to perform this surgery.

In our study, immediate postoperative pain was prophylactically dealt by this study [13]. Pain was assessed using a Wong Baker Faces rating scale (WBF). Using the adequate analgesia for pain management, according to world health organization (WHO) guidelines our aim was to keep the WBF score below 3. Analgesia administered on the basis of WBF scale [14]. In our study, postoperative pain (WBS scale >/=3) incidence was 68% in Group A and only 12% in Group B. (P value 0.00021). Thus, Chivate`s hemorrhoidopexy is better for postoperative pain than Milligan Morgan`s technique. Adil Shaker study (2018) for 190 patients, in which 80.1 % patients had pain postoperatively [15]. Both the suture lines are above the dentate line, pain is reduced drastically due to no somatic sensation in this area in hemorrhoidopexy [16]. Postoperative pain is the major drawback in hemorrhoidectomy. Because of above reasons Chivate`s hemorrhoidopexy is becoming widely acceptable procedure due to less patient discomfort.

Postoperative bleeding was statistically analysed which showed 12% incidence of bleeding in hemorrhoidopexy as compared to 36% in hemorrhoidectomy (p value 0.0473). To note, in this study, bleeding was assessed by subjective method, based on patient`s complaints. Thus, chivate`s procedure is better

in terms of intraoperative and postoperative bleeding than open hemorrhoidectomy. In Milligan Morgan`s hemorrhoidectomy, the bleeding is due to early separation of the ligated pedicle before adequate thrombosis in the feeding artery can occur [17]. It needs to be controlled either by returning to theatre for suture ligation or at bedside by anal packing or tamponade effect by folley`s catheter. This complication is least encountered in suture hemorrhoidopexy. adil saker study, observed 56 % incidence of postoperative bleeding in hemorrhoidectomy group which is comparable to our study [15].

Hospital in stay was studied and statistical analysis was done. With reference to patients discharged in 2 days, 24% were discharged in Group A and 84% patients in Group B. Calculated P value was 0.035015. Chivate`s hemorrhoidopexy requires lesser hospital in stay compared to hemorrhoidectomy and thus patient can return to daily work earlier. Dr Chivate undertook a study in which, it was observed that open hemorrhoidectomy is very painful requiring 3-5 days hospital in stay. Due to less pain post operatively hemorrhoidopexy needs less hospital in stay [19]. Another study with comparable results, Neeralagi CS et al (2017), in 120 patients found that the mean hospital in stay for hemorrhoidectomy is 4.1 days [18].

Recurrence at follow up was studied, revealed that 6.67 % patients had recurrence in patients who underwent open hemorrhoidectomy against 40% in patients who underwent suture hemorrhoidopexy. Statistics signified it with P value 0.002271. To state, Chivate`s procedure is better in outcome compared to Milligan Morgan`s surgery as there is less recurrence and better satisfaction of patient in this regard. Hemorrhoidectomy is based on the principle of minimization of loss of skin and the mucosa of the anal canal that bridges between the two excised hemorrhoids to prevent stricture. Haemorrhoidal arterial ligation (HAL) is done to occlude blood supply. But afterwards, the smaller feeders, as collaterals forms, which is summarized as to be the potential cause of the recurrence of 18-25 %. In contrast to this, in hemorrhoidopexy, circumferential blockage at two sites the distance of 2 cm, decreases the development of the collaterals and so as recurrence. Another theory for recurrence in hemorrhoidopexy group, is supposed to be due to inadequate suture bite at appropriate depth (inadequate hemorrhoidopexy) [19]. Sakr et al (2009) total 45 patients hemorrhoidectomy concluded the recurrence rate of 9.16 % [20]. Similarly in terms of recurrence Kim et al had 24 % incidence [21]. We need higher number of patients to study and compare in both the groups to provide acceptable results on larger basis. It is advisable to perform the study for longer duration (in years).

Conclusion

To conclude, transanal suture hemorrhoidopexy (Chivate`s procedure) resulted in less post operative bleeding, lesser pain, decreased requirement of analgesia, earlier ambulation, with easier and sooner return to daily life with minimal secondary complications in forms of anal stricture and bleeding with improvable operative time, decreased hospital in stay, compared to hemorrhoidectomy (Milligan Morgan`s technique). Thus, Chivate`s hemorrhoidopexy can be recommended as a safer and better alternative surgery than Milligan Morgan`s open surgery after adequate training.

Recommendation

We need higher number of patients to study and compare in both the groups to provide acceptable results on larger basis. It is advisable to perform the study with longer follow up (in years)..

Acknowledgments

With the permission of Dean and Superintendent of tertiary care hospital of south Gujarat.

Conflicts of interest

The authors declares that they do not have conflict of interest.

References

1. Loder PB, Kamm MA, Nicholls RJ, Phillips RK: Haemorrhoids: pathology, pathophysiology and aetiology. Br J Surg 1994; 81: 946–954. DOI: 10.1002/bjs.1800810707.
2. Keighly MRB, Williams NS. Surgery of the Anus, Rectum and Colon, 1999. New York: WB Saunders, 1999.
3. Guttenplan M, Ganz RA. Hemorrhoids: office management and review for gastroenterologists. Available from: URL: http://Touchgastroentorology.com. Accessed December 2011.
4. Han W, Wang ZJ, Zhao B, Yang XQ, Wang D, Wang JP, Tang XY, Zhao F, Hung YT. Pathologic change of elastic fibers with difference of microvessel density and expression of angiogenesis-related proteins in internal hemorrhoid tissues. Zhonghuaweichang Waike Zazhi 2005; 8: 56–59.
5. Thompson WH. The nature of hemorrhoids. Br J Surg. 1975; 62: 542.
6. MacRae HM, McLeod RS. Comparison of hemorrhoidal treatment modalities. A meta-analysis. Dis Colon Rectum 1995; 38: 687–694. DOI: 10.1007/BF02048023
7. Longo A. Treatment of hemorrhoids disease by reduction of mucosa and haemorrhoidal prolapse with a circular suturing device: A new procedure. Proceedings of the 6th World Congress of Endoscopic Surgery; 1998 June 3-6; Rome, Italy.
8. Perrotti P, Dominici P, Grossi E, et al. Topical nifedipine with lidocaine ointment versus active control for pain after haemorrhoidectomy: results of a multicentre, prospective, randomized double-blind study. Can J Surg. 2010; 53(1): 17–24.
9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675080/
10. Milligan ET, Morgan CN, Lond LE. Surgical Anatomy of anal canal, and the operative treatment of hemorrhoids. Lancet. 1937; 2: 1119.
11. https://wongbakerfaces.org
12. Dinesh P. Sagar P.suture hemprrhoidopexy vs open hemorrhoidectomy: comperative study of post operative complications: 2020; 9(1): 2277–2279.
13. https://speciality.medicaldialogues.in/french-society-of-anesthesia-guidelines-on-postoperative-pain-management/
14. https://www.who.int/news-room/detail/27-08-2019-who-revision-of-pain-management-guidelines
15. https://www.ijmrhs.com/medical-research/classical-milligan-morgan-hemorrhoidectomy-versus-its-modification-higher-risk-of-fistula-and-mucosal-ectropion.pdf
16. Rosen L, Sipe P, Stasik JJ, et al: Outcome of delayed hemorrhage following surgical hemorrhoidectomy. Dis Colon Rectum 1993; 36: 743.
17. Neeralagi CS et al. Int Surg J. 2017; 4(10): 3358–3362.
18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3477406/
19. Sakr MF. LigaSure versus Milligan-Morgan hemorrhoidectomy: a prospective randomized clinical trial. Tech Coloproctol 2010; 14: 13–17. DOI: 10.1007/ s10151-009-0549-4
20. Kim JS, Vashist YK, Thieltges S, Zehler O, Gawad KA, Yekebas EF, Izbicki JR, Kutup A. Stapled hemorrhoidopexy versus Milli-gan-Morgan hemorrhoidectomy in circumferential third-degree hemorrhoids: long-term results of a randomized controlled trial. J Gastrointest Surg. 2013; 17(7): 1292–1298. DOI: 10.1007/s11605-013-2220-7.

National Board of Examination - Journal of Medical Sciences
Volume 1, Issue 3, Pages 151–164, March 2023
DOI 10.61770/NBEJMS.2023.v01.i03.005

ORIGINAL ARTICLE

Breast Diseases: Role of Gynaecologist Present and Future - An Indian Scenario

Umare Mangesh B[1,*] and Rajurkar Dhanshree B

[1]*Consultant, Obstetrics & Gynaecology, Pune, India*
[2]*Senior Resident, Department of Obstetrics & Gynaecology, PCMC'S Postgraduate Institute Y.C.M. Hospital. Pimpri, Pune, India*

Accepted: 06-February-2023 / Published Online: 01-March-2023

Abstract

During the life period of a female, female breast as organ is undergo constant physical and physiological changes that are related to puberty, the menstrual cycle, pregnancy, lactation, and menopause. It has always been an emblem of womanhood**,** an important part of female reproductive system that influences Body image & Sexual function.

Either benign or malignant, any breast lesion is a cause of concern for patients even talking about the breast related conditions is considered a taboo in Indian society, that's why As compared to developed world where 70% cases diagnosed in early stage, in India only 30% cases reported in early stages.

In the context of the Indian scenario, Indian women feel comfortable talking about reproductive organs and relating queries including the breast related ones to obstetricians and gynaecologists irrespective of the gender of the treating physician, and in return, women expect to have their treating physician expert in, evaluation diagnosis, and management of breast problems that arise from self-examination, routine mammography, any unusual breast symptoms, or any unusual breast lump during routine gynaecology examinations.

Key words: female breast diseases, gynaecologist, screening, Indian scenario

*Corresponding author: Umare Mangesh B
Email: mangeshumre0963@gmail.com

Introduction

Breast disease is as important as any other women's health issue and Obstetrics & Gynaecologic examination is incomplete without examination of the breasts. The gynaecologist act as specialist as well as the primary physician, and sometimes the only physician for the woman of all ages especially childbearing age and also for the woman after menopause.

Gynecologists by the very nature of their practices, are in an excellent position to find breast lesions than by any other physician. In Europe, and many parts of the world the surgically trained gynaecologist in breast diseases take part not only in detection and diagnosis as well as in the management i.e. surgical and medical treatment [1].

Mass screening campaign in the United States of America, clinical and mammographic screening of tens of thousands of women, could detect cancer 'early' and reduce mortality in screened groups proved to be [2].

The global prevalence of breast cancer is projected to exceed 2 million by 2030, with developing countries being the largest contributors. For India, incidence rates vary across the country, with the northeast and metropolitan areas (Mumbai, New Delhi) showing the highest rates [3].

Aim & Objective

1. To give picture about prevalence of female breast disease in respective region of India.
2. To make suggestions for the inclusion of Teachings on female breast diseases and mammography into the obstetrics and gynaecology residency curriculum so that residents have the skills to perform breast cyst aspiration, breast biopsy (incision or excision), and guided biopsy of nonpalpable lesions.
3. To make suggestion for inclusion of Post Graduate Obstetrics & Gynecology Specialist in breast surgery fellowships teaching program.

Prevalence of Breast Diseases in India

Method

We have gone through various latest research article to give present burden of breast diseases in India.

Benign and Malignant Breast Diseases

Burden of Benign Breast Diseases

Benign breast disease is the main explanation for breast problems.

About a quarter of women will have a benign breast condition that requires treatment at some point in their lives. Benign breast disease accounts for the majority of breast complaints and yet is largely ignored [4].

Benign lesions of the breast require attention due to their high prevalence, impact on women's lives, and potential cancer in some histological types [5] (Figure 1).

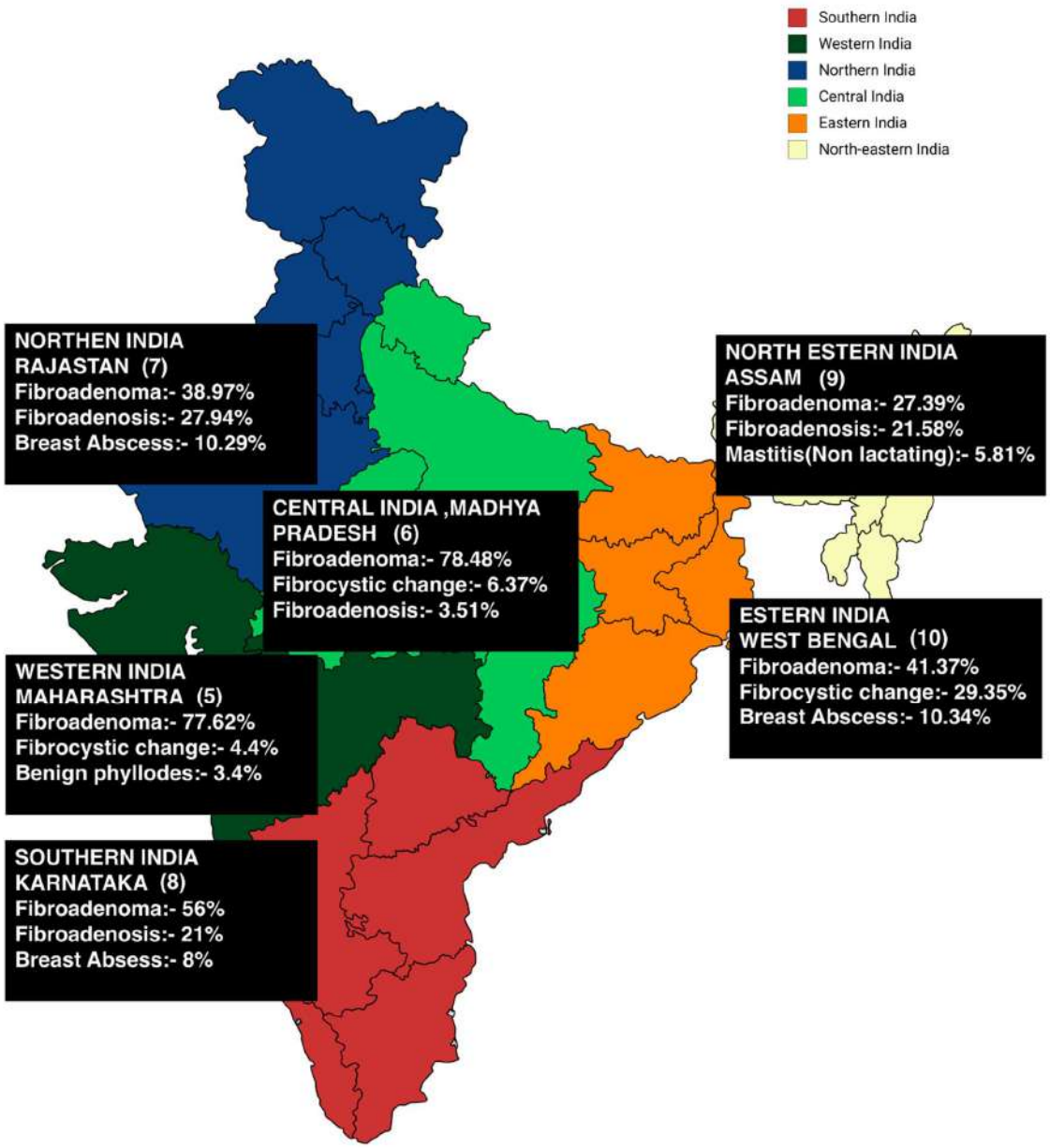


Figure 1. This map statistic shows the pattern & prevalence of benign breast diseases in different parts of India

Burden of Malignant Breast Disease

Number (n) and relative proportion (%) of gynaecologic cancers, including breast cancer, associated with all cancer foci in women. National Cancer Registry Program, 2021. (Table 1).

Table 1. Report of Hospital-Based Cancer Registry, 2021, National Cancer Registry Program [11].

Site of cancer	No. of cases	% of cases
Breast	*73,998*	*25.4*
Cervix Uteri	44,300	15.2
Corpus Uteri	7,648	2.6
Ovary	18,411	6.3
Other Gynecological Cancers	3,981	1.4
Vulva	1,112	0.4
Vagina	1,749	0.6
Uterus part unspecified	691	0.2
Fallopian tube	216	0.1
Placenta	213	0.1
Gynecological cancers including breast cancer	1,48,338	51.0
All sites of cancer in women	2,90,986	100.0

Table 2. Breast Cancer -histological classification & Proportion (%) [11].

Broad histological classification	% of cases
Epithelial tumours	
Infiltrating duct carcinoma	89.7
Lobular carcinoma	1.8
Papillary carcinoma	0.5
Carcinoma, NOS	4.1
Fibroepithelial tumours	
Phyllodes tumour	0.6
Mesenchymal tumours	
Sarcoma	0.2
Others	3.1
Total	100.0

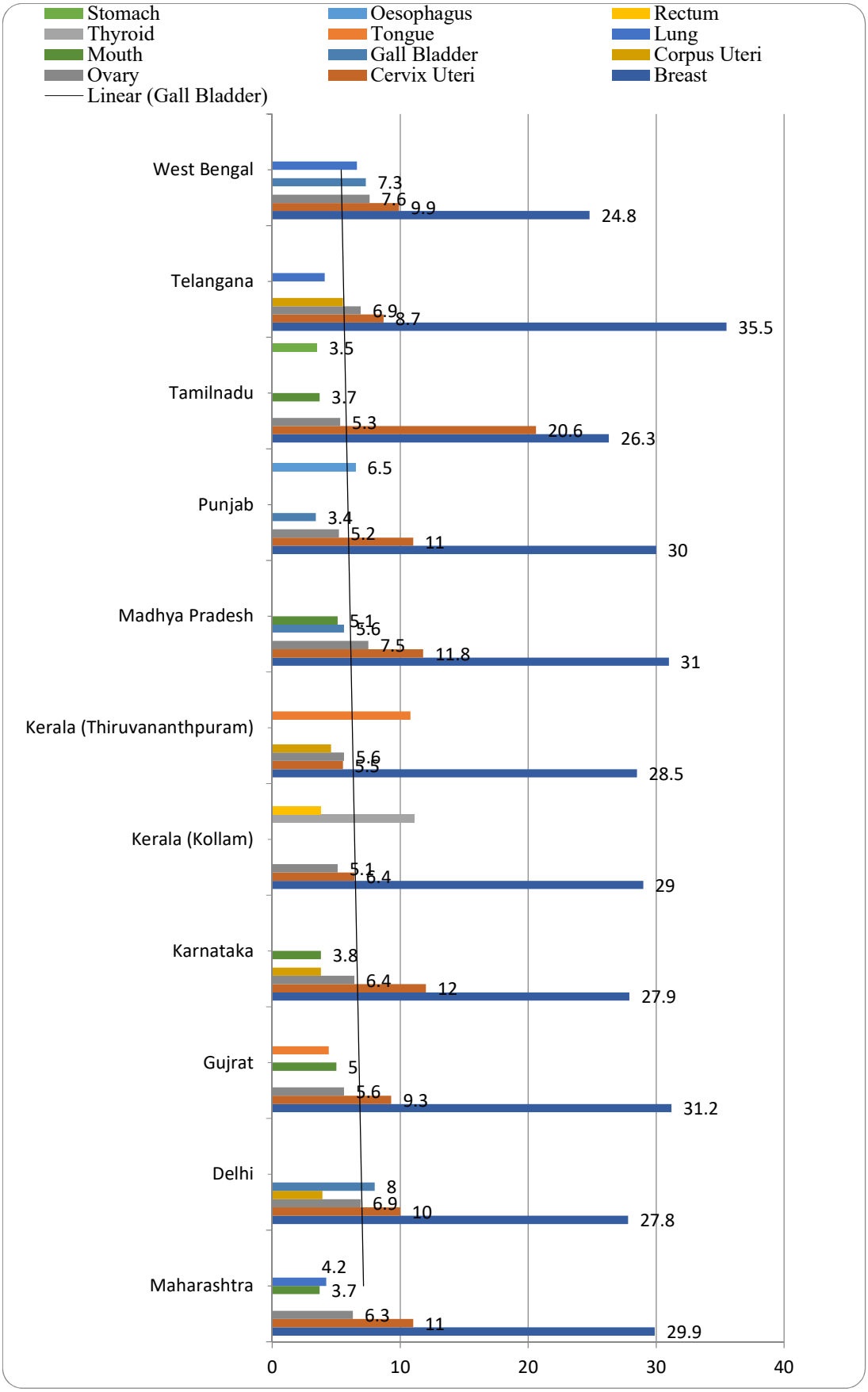


Figure 2.State wise Five Leading Sites of Cancers among females, ICMR- Bengaluru. 2021 [12].

Table 3.The projected cases of cancer in India in 2020 and in 2025 are shown in the table below [13].

Cancer Classified According To Broad Anatomical Sites	**2020**		**2025**	
	No. of Cases	**(%)**	**No. of Cases**	**(%)**
All Sites	**13,92,179**	**100.0**	**15,69,793**	**100.0**
Tobacco Related Cancers	3,77,830	27.1	4,27,273	27.2
Gastro Intestinal Tract	2,73,982	19.7	3,10,142	19.8
Breast	*2,05,424*	*14.8*	*2,32,832*	*14.8*
Lymphoid &Haematopoietic Malignancies	1,24,931	9.0	1,38,592	8.8
Cervix Uteri	75,209	5.4	85,241	5.4
Corpus Uteri and Ovary	70,400	5.1	79,765	5.1
Prostate	41,532	3.0	47,068	3.0
Central Nervous System	32,729	2.4	36,258	2.3

World Body on Breast Cases in India [14]

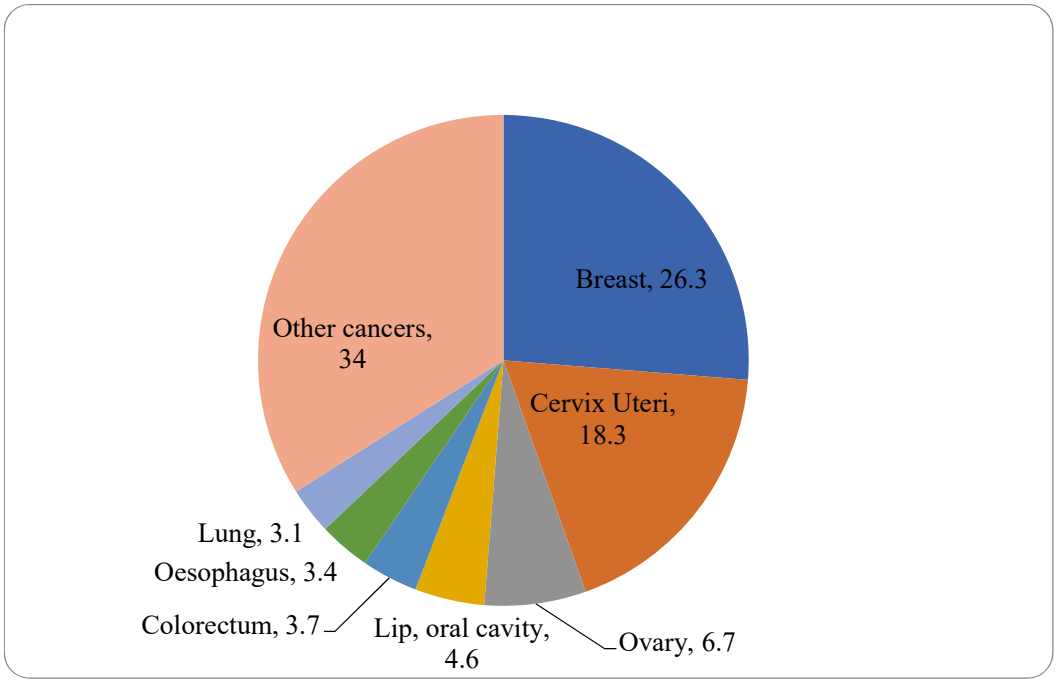


Figure 3. Estimated number of cases in 2020, India, females all ages (Total cases 6,78,383)

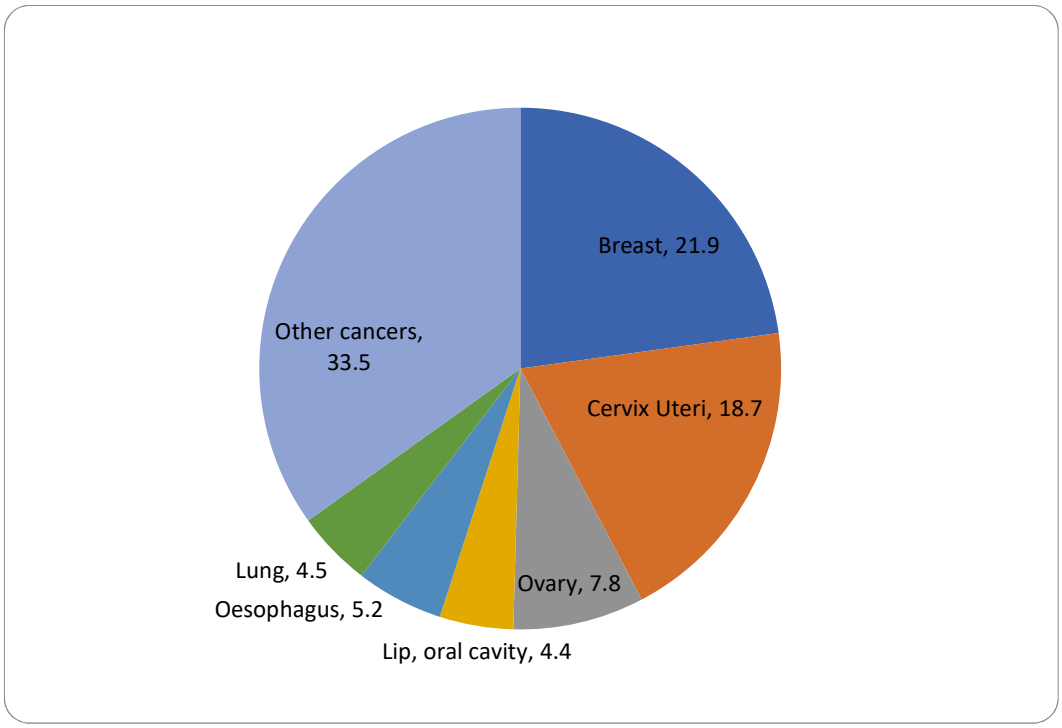


Figure 4. Estimated number of deaths in 2020, India, females all ages (Total cases 4,13,381)

Burden of Cancer Breast in World [14]

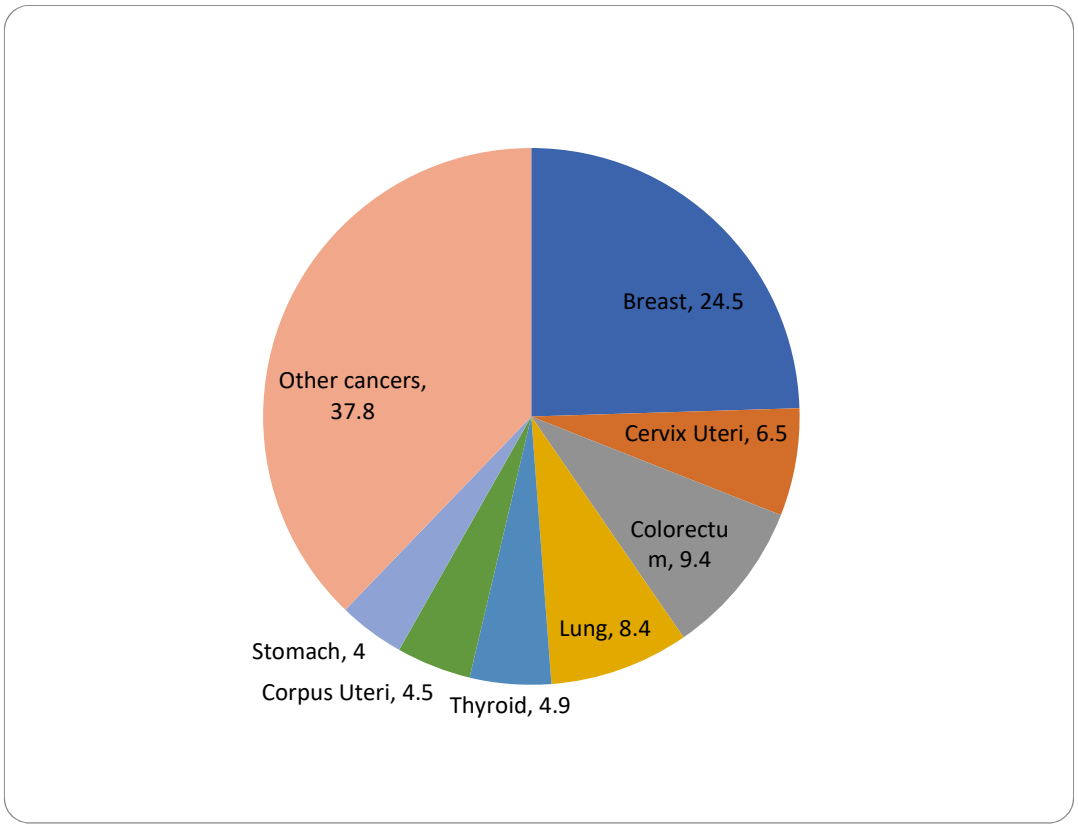


Figure 5. Estimated Worldwide number of cancer cases in 2020, females all ages (Total cases 92,27,484)

Education about screening of breast cancer among women in different states of India [15].

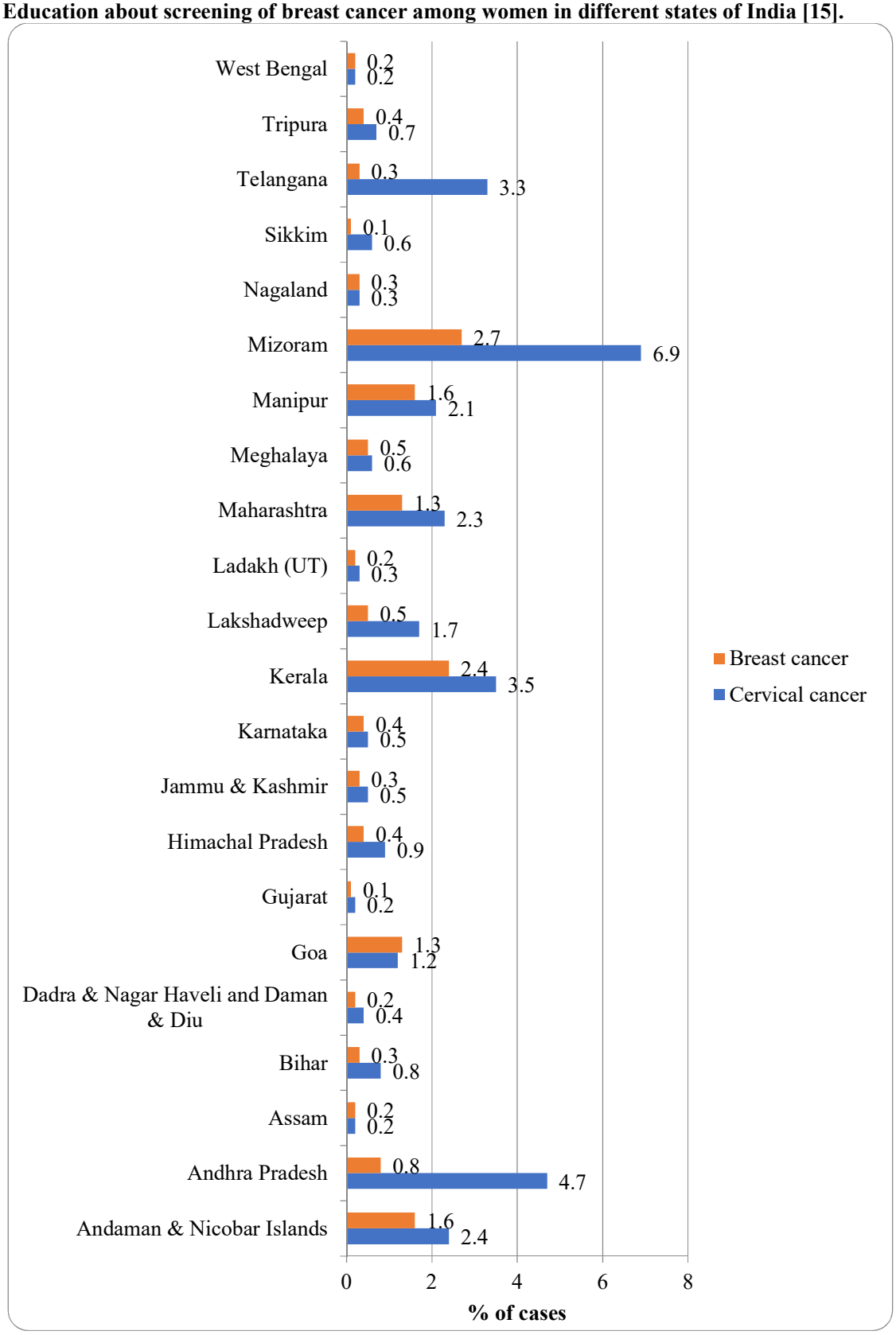


Figure 6.Screening Of Breast Cancer And Cervix Cancer, (Age 30–49 Years). Nfhs-5 (2019–20), NFHS-5 (2019–20)

Role played by gynaecologist at present in preventing oncology for breast cancer and related diseases.

1. Act as primary source of information for a women regarding the breast related diseases and complaints.
2. Taking detailed history of any breast diseases at present, in past or in family and categorising the woman at risk for developing cancer breast or not
3. Doing clinical examination of breast.
4. Teaching about "self -breast examination" and awareness about breast health to woman who come to gynaecology OPD for various gynaecological problems. We can correctly termed as *"opportunistic patient education."*
5. Alleviate the breast diseases related anxiety in a woman.
6. Treatment of minor breast related ailments during pregnancy and lactation.
7. Discriminating grossly on the basis of history and clinical examination between probable benign or malignant disease of disease and appropriate referral.
8. Various committees of gynaecologists e.g. FOGSI involved in organising mass screening camps for breast cancer along with cervical cancer.

Why it is a Need of Hour?

To include teachings of female breast diseases and mammography in the residency teaching program of obstetrics and gynecology.

And

Inclusion MS/DNB trained gynecologist in breast surgery fellowships teaching program.

And the Answer is

Breast cancer in India is reaching at an alarming rate, so a more educated workforce is needed to solve the problem of breast disease [16].

Statistics and Scientific Facts About Breast Cancer.

Statistics

- In India breast cancer is diagnosed in 1 woman with a passage of every 4 minutes.
- In India 1 woman dies of Breast cancer, every passing 8 minutes.
- In womans lifetime out of 28 women 1 women is expected to develop breast cancer in her lifetime.
- India's population is overwhelmingly young, so the number of women diagnosed with breast cancer will continue to increase in this age group.
- India has the highest incidence of triple-negative breast cancer, the most aggressive form of breast cancer in the world.
- An estimated 1,62,468 women were newly diagnosed with breast cancer in India in 2018. In 2018, 87,090 women died of breast cancer in India. This was the second-highest number in the world for that year.
- By the year 2030, most deaths among women in India will be caused by breast cancer than any other disease.
- Compare to the United States of America, 90 percent of women with breast cancer survive five years; whereas in India, only 66 percent survive.
- About 50% of breast cancer patients first see a doctor when they are at stage 3, and 15-20% of patients see a doctor when they are at stage 4. the 10-year survival rate for a woman with breast cancer is 75% in stage 1, whereas survival decreased to 5% in stage 4 patients.
- A Comprehensive modelling study on the impact of the COVID-19 pandemic on surgery predicted that 59.7% of cancer surgeries in India were postponed during the peak of 12 weeks, with 51,100 cancer surgeries postponed. Nearly 50% of all cases are in his 25–50 year-old group.

According to authors following are some of Facts/problems and we have suggested solutions

Fact/Problem

Breast cancer is fast developing into a public health crisis, and uneasiness in society to talk about women's breast health is exacerbating the situation even more.

Solution

Gynecologists by the very nature of their practices, are in an excellent position to find breast lesions than by any other physician. The most applicable/ pragmatic screening modality for breast cancer in Indian scenario is clinical breast examination (60%), compared to breast self-examination which is only 20% [17].

In Europe, and many parts of the world the surgically trained gynaecologist in breast diseases take part not only in detection and diagnosis as well as in the management i.e. surgical and medical treatment [1].

In India we need to apply same strategy to tackle public health crisis of breast cancer and breast related diseases.

Fact
In pregnancy, breast examination is an integral part of antenatal check-up, and is incomplete without breast examination

Solution
Obstetrics & gynaecology specialist takes this opportunity to detect previously un-noticed breast lesion by women, results in earliest intervention.

Fact
It is an established fact that Women who ever used oral contraceptives/hormone replacement therapy were found to have a slightly (7%) increased relative risk of breast cancer compared with women who never used oral contraceptives [18].

Solution
Women using oral contraceptives/hormone replacement therapy will present first to gynaecologist or breast lesion in women using oral contraceptives/hormone replacement therapy will be identified or suspected by gynaecologist than any other specialist.

Obstetrics & gynaecology specialist trained in breast diseases and surgeries will take appropriate intervention on time, in women using oral contraceptives/hormone replacement therapy.

Fact
Characteristic of hereditary breast cancer especially those associated with BRCA-1 & BRCA-2 and ovarian cancer i.e. HBOC is that these female patients are at increased risk of female breast cancer, and ovarian cancer including fallopian tube and primary peritoneal cancers. and these female patients are primarily present to gynaecologists[19].

Solution
Obstetrics & gynaecology specialist trained in breast diseases and surgeries

According to oncological consideration:-

will perform bilateral mastectomy as a primary surgical treatment of breast cancer because of elevated rate of ipsilateral and contralateral breast cancer [19].

According to preventive principles:-

Will perform Prophylactic bilateral mastectomy, prophylactic oophorectomy, and chemoprevention (e.g., tamoxifen) [19].

Fact/Problem
Breast cancer is a treatable disease, and early detection increases the chances of survival. The simplest reason women don't seek treatment early is that breast most lumps are painless.

Solution
Opportunistic patient education by gynaecologist, trained gynaecology resident in diagnostic biopsies and teachings of mammography.

Fact/problem
According to the 2020 World Cancer Report, the most effective breast cancer control intervention is early detection. Breast cancer has a low survival rate because it is detected late.

Solution
Addition of more trained personnel by training gynaecology residents in breast biopsies(incisional or excisional), guided biopsy for nonpalpable lesions, teachings of mammography and Inclusion MS/DNB trained gynecologist in breast surgery fellowships teaching program.

Fact/problem
There are cases in rural and in some urban medical facilities, Treatment of breast diseases by poorly trained medical professionals can lead to delayed diagnosis, increased costs due to complications, worse overall outcomes, and psychological distress for patients and families

Solution

Training gynaecology resident and MS/DNB trained gynaecologist will advantageous in fallowing ways.

a) Will add number of trained personnel in the pool of breast care provider.
b) At present in residency teaching program of obstetrics and gynecology USG teachings is included it can be taken advantages of in, e.g. For the guided biopsy, identification of lump and it's characteristics.
c) The breasts are part of the female reproductive system and is in the scope of obstetrics and gynaecology examination, If any suspicious looking lump is found during gynaecologic exam in woman with high risk can be biopsied without delay in the diagnosis.
d) Early diagnosis not only improves outcomes but can also significantly reduce treatment costs.

Breast Education in India

Guidelines by Two boards of Indian medical education on breast diseases.

A) What National Medical Commission (formerly MCI) recommend about breast disease teaching in residency programme of obstetrics and gynaecology

Subject Specific Competencies:

At the end of the MS Obstetrics and Gynaecology course, students should have mastered the following: Basic knowledge of female breasts and their disorders.

B) What National Board Of Examinations (NBE) recommend.

Goal

Elementary knowledge of female Breast & its diseases.

Is There Any Breast Fellowship in India Which Train Gynaecology Speciality in Breast Surgery?

NO

Is There Any Breast Fellowship Internationally, Europe USA and Middle East Which Train Gynaecology Speciality in Breast Surgery?

YES

WORLD

INTERNATIONAL

The Senologic International Society (SIS), International School of Senology, France
SIS Fellowship in Breast Surgery.
(Reference-respective website of the institute)

Eligibility

A Board Certified General Surgeon or Gynecologist.

Europe

The Breso-European Breast Surgical Oncology Certification
Jointly formed in 2019 by the fallowing organisations [20].

1. The European Society of Surgical Oncology(ESSO)
2. The European Society of Breast Cancer Specialists (EUSOMA)
3. The Division of Breast Surgery of the European Board of Surgery of the European Union of Medical Specialists (UEMS)
4. The European School of Oncology (ESO)
5. The European Breast Cancer Research Association of Surgical Trialists (EUBREAST)
6. The Central-Eastern European Breast Cancer Surgical Consortium (CEEBCSC)
7. The Group for Reconstructive and Therapeutic Advancements (G.Re.T.A)

Deliver training in following countries

1. United Kingdom
2. France
3. Germany
4. Italy
5. Sweden
6. Switzerland
7. Poland
8. Turkey

9. Spain
10. Belgium
11. Ireland
12. Ukraine
13. Portugal
14. Hungary
15. Finland

Eligibility/Requirement:-The BRESO certification programme can be undertaken during or following completion of standard general, gynaecological or plastic surgery training

United States of America

There is variation eligibility for breast fellowship programmes in America following are centres which train the gynaecology speciality in breast surgery.

(Reference-respective website of the institutes)

1. The Massachusetts University Medical School.

Eligibility:-Board Certified general surgery or OB/GYN .

2. Texas Tech University Health Science Center breast fellowship.

Eligibility: Surgery & Obstetrics and Gynaecology.

3. Women and Infants Hospital Providence, Rhode Island.

Eligibility: Surgically-trained in general surgery, ObGyn, plastics.

4. Cedars-Sinai Non-profit hospital – Los Angeles.

Eligibility: Board-certified candidates who have completed a general surgery or obstetrics-gynaecology residency.

5. Dana-Farber Cancer Institute and Brigham and Women's Hospital, Massachusetts General Hospital.

Eligibility: Applicants must be ACGME-accredited general surgery and/or gynecology.

6. Vassar Brothers Medical Center at Nuvance Health

Eligibility: certified by the American Board of Surgery, the American Board of Obstetrics and Gynaecology.

7. University of Southern California (USC)

Eligibility: General surgery, Obstetrics/Gynecology and Plastic/Reconstructive surgery

Middle East

Tehran University of Medical Sciences
(Reference-respective website of the institute)

Department of Breast Cancer Surgery Training Program

Eligibility: Board-certified Gynecologic or General Surgeons

Advantages of inclusion procedure of breast (incisional or excisional), guided biopsy, and teachings of mammography in residency teaching program of obstetrics and gynecology

&

Inclusion gynecologist in breast surgery fellowships teaching program.

1. Will add number of trained personnel in the pool of breast care provider.
2. At present in residency teaching program of obstetrics and gynecology USG teachings is included it can be taken advantages in, e.g. For the guided biopsy, identification of lump and it's characteristics.
3. The breasts are part of the female reproductive system and is in the scope of obstetrics and gynecology examination, if any suspicious looking lump is found during gynaecologic exam in woman with high risk can be biopsied without delay in the diagnosis.
4. Early diagnosis not only improves outcomes but can also significantly reduce treatment costs.

Experience of other countries regarding breast teachings in obstetrics and gynaecology residency

1) A breast clinic in a Department of Obstetrics and Gynecology [21].

William H Hindle MD ,Daniel R Mishell Jr MD, Raquel D Arias MD, Susana G Gonzalez MD, Barbara D Florentine MD.

2) The impact of a gynecology breast clinic and curriculum on the management of breast disease following residency [22].

Michelle Quaye MD, Gary Glasser MD.

3) A gynecology department breast clinic: the first year [23].

David Damrich MD, Gary Glasser MD, Mary Dolanmd, MPH

4) Fine Needle Aspiration of Palpable Breast Masses Performed in a Military Obstetrics/Gynecology Clinic: A Follow-Up Report [24]

C. Wittich, MC USA, Eric R. Salminen, MC USA, Romeo P. Perez, MC USA

Conclusion

Hesitancy among Indian women to talk about Breast related diseases Is Fast Becoming a Costly Taboo in India.

Obstetricians and gynaecologists are the primary providers of women's health maintenance, and reproductive organs including of breast related education and general health screening for the woman, And now it is the need of the hour to involve the specialty of obstetrics and gynaecology in the diagnosis, management, and cancer care of breast.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

This research study received no funding from any agency or organization.

References

1. Gusberg SB. The gynecologist and breast cancer. Israel journal of medical sciences. 1981; Sep 1; 17(9–10): 843–6. https://pubmed.ncbi.nlm.nih.gov/7309470/
2. Jallut O, Hessler C. Usefulness of detection of breast cancer: the part played by the internist. Schweizerische Medizinische Wochenschrift. 1976; Jul 1; 106(27): 918–22. https://europepmc.org/article/med/996512
3. Gupta A, Shridhar K, Dhillon PK. A review of breast cancer awareness among women in India: Cancer literate or awareness deficit?. European Journal of Cancer. 2015; Sep 1; 51(14): 2058–66. https://www.sciencedirect.com/science/article/pii/S0959804915006656
4. Selvakumaran S, Sangma MB. Study of various benign breast diseases. International Surgery Journal. 2016; Dec 13; 4(1): 339–43. http://dx.doi.org/10.18203/2349-2902.isj20164466
5. Hatim KS, Laxmikant NS, Mulla TJ. Patterns and prevalence of benign breast disease in Western India. Int J Res Med Sci. 2017; Feb;5(2):684-8. https://dx.doi.org/10.18203/2320-6012.ijrms20170174
6. Jain R, Sahu KK, Magnani KK, Mangal KS. Burden of Breast lesions in Females in Gwalior region–A 3 yr retrospective study. https://www.ijhcr.com/index.php/ijhcr/article/view/1207/1016
7. Bharti Saraswat, Anant Vyas, Clinicopathological Profile of Benign Breast Disease at a Tertiary Care Hospital in Western Rajasthan, Indian Journal of Applied Research: 2017; 7(5). https://www.worldwidejournals.com/indian-journal-of-applied-research-(IJAR)/fileview/May_2017_1493641200__25.pdf
8. Abhijit MG, Anantharaman D, Bhoopal S, Ramanujam R. Benign breast diseases: experience at a teaching hospital in rural India. https://www.msjonline.org/index.php/ijrms/article/view/2562
9. Dhirendra Nath Choudhury, Anjai Kumar Baishya, An Analytical Study of Benign Breast Disease, Indian Journal of Applied Research, 216; 6(9). https://www.worldwidejournals.com/indian-journal-of-applied-research-

(IJAR)/fileview/September_2016_1492161039__170.pdf
10. Bhar A, Karmakar S, Mukherjee S, Medinipur P, Bengal W. Clinico Pathological Study of Benign Breast Lump– A Hospital Based Study. Breast. 2: 3–44. https://www.jebmh.com/articles/clinico-pathological-study-of-benign-breast-lump--a-hospital-based-study.pdf.pdf
11. Clinicopathological Profile of Cancers in India: A Report of the Hospital .Based Cancer Registries, 2021,National Cancer Registry Programme. https://ncdirindia.org/All_Reports/HBCR_2021/resources/HBCR_2021.pdf]
12. State Wise Factsheet, ICMR-National Centre for Disease Informatics and Research, Bengaluru.2021. https://ncdirindia.org/All_Reports/State_Factsheet_21/default.aspx
13. Report of National Cancer Registry Programme (2012-2016) Bengaluru, India 2020. https://www.ncdirindia.org/All_Reports/Report_2020/resources/NCRP_2020_2012_16.pdf
14. GLOBOCAN 2020: New Global Cancer Data. https://www.uicc.org/news/globocan-2020-new-global-cancer-data
15. National Family Health Survey (NFHS-5), 2019–20. http://rchiips.org/nfhs/factsheet_NFHS-5.shtml
16 Breast Cancer India. https://www.breastcancerindia.net/
17. Somashekhar SP, Deo SV, Sarkar D, Ashwin KR, Kumar CR, Kaur N, Jain S, Pillarisetti R. Association of Breast Surgeons of India (ABSI) Practical Consensus Statement, Recommendations, and Guidelines for the Treatment of Breast Cancer in India 2021—Indian Solutions for Indian Problems. Indian Journal of Surgery. 2022; Oct; 84(3): 573–84. https://doi.org/10.1007/s12262-021-03160-y
18. Oral Contraceptives and Cancer Risk, National Cancer Institute. https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/oral-contraceptives-fact-sheet#r4
19. Petrucelli N, Daly MB, Pal T. BRCA1-and BRCA2-associated hereditary breast and ovarian cancer. https://www.ncbi.nlm.nih.gov/books/NBK1247/pdf/Bookshelf_NBK1247.pdf
20. Breso Website. https://breastsurgeoncertification.com/
21. Hindle WH, Mishell Jr DR, Arias RD, Gonzalez SG, Florentine BD. A breast clinic in a Department of Obstetrics and Gynecology. Obstetrics & Gynecology. 1999; Jun 1; 93(6): 1044–8. https://doi.org/10.1016/S0029-7844(98)00576-6
22. Quaye M, Glasser G. The impact of a gynecology breast clinic and curriculum on the management of breast disease following residency. Primary Care Update for OB/GYNS. 1999; Nov 1; 6(6): 197–201. https://doi.org/10.1016/S1068-607X(99)00024-4
23. Damrich D, Glasser G, Dolan M. A gynecology department breast clinic: The first year. Primary Care Update for OB/GYNS. 1997; Nov 1; 4(6): 247–50. https://doi.org/10.1016/S1068-607X(97)00106-6
24. Wittich AC, Salminen ER, Perez RP. Fine needle aspiration of palpable breast masses performed in a military obstetrics/gynecology clinic: A follow-up report. Military medicine. 1997; Oct 1; 162(10): 680–2. https://doi.org/10.1093/milmed/162.10.680

National Board of Examination - Journal of Medical Sciences

Volume 1, Issue 3, Pages 165–170, March 2023

DOI 10.61770/NBEJMS.2023.v01.i03.006

ORIGINAL ARTICLE

Pseudocyst of Pinna: Recurrence free Approach with drain placement - A Tertiary care Experience

Varunkumar J[1,*] and Priyanka Kumar Arora[2]

[1]*Department of Otorhinolaryngology, Sri Venkateshwaraa Medical College Hospital & Research Centre, Ariyur Puducherry, Tamilnadu 605102, India*

[2]*Department of Otorhinolarynogology, Topiwala National Medical College, Mumbai Central, Mumbai-400008, India*

Accepted: 5-February-2023 / Published Online: 01-March-2023

Abstract

Background: Pseudocyst (seroma) of pinna is a clinical condition where there occurs accumulation of serous fluid between the skin and perichondrium layer either due to trivial trauma or degeneration. Treatment of this condition is challenging as there are high chances of recurrence and cosmetic disfigurement.

Methodology: 20 clinically diagnosed auricular seroma patients were studied and compared with needle aspiration technique & Incision and drainage with drain in situ technique and results were compiled.

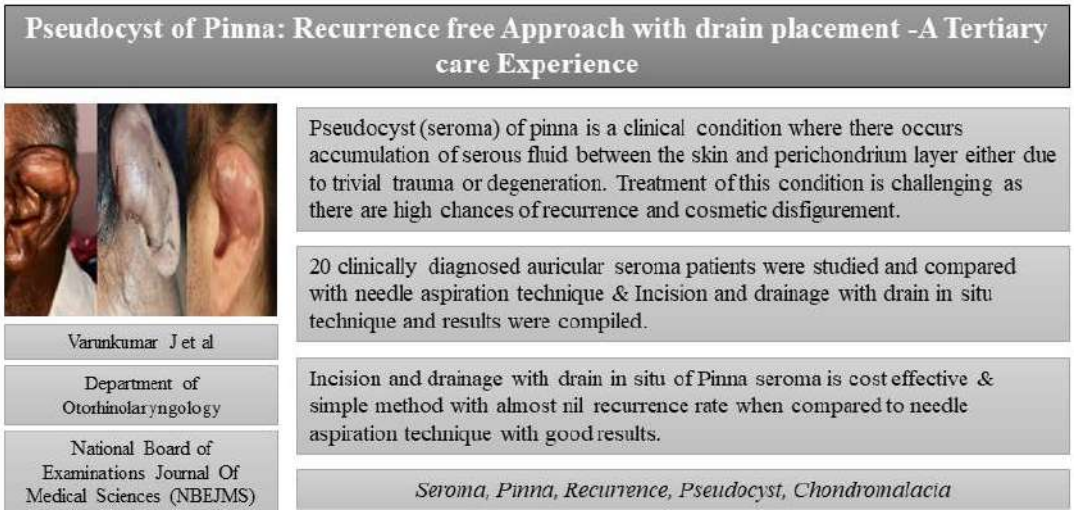
Results: All patients tolerated procedure well. Patients who underwent needle aspiration and pressure dressing had 40% recurrence when compared to drain in situ technique with no recurrence and disfigurement of pinna on follow up of 6 months.

Conclusion: Incision and drainage with drain in situ of Pinna seroma is cost effective & simple method with almost nil recurrence rate when compared to needle aspiration technique with good results.

Keywords: Seroma, Pinna, Recurrence, Pseudocyst, Chondromalacia

*Corresponding author: Varunkumar J
Email: varun.jvk@gmail.com

Graphical Abstract



Introduction

Pinna seroma is an uncommon, painless swelling of pinna not associated with signs of inflammation until infected characterised by enchondral cyst formation [1]. The etiopathogenesis of the disease still remains inconclusive. Hartmann in 1846 reported this condition first followed by 12 intracartilagenous cyst. Engel in 1966 coined the term auricular pseudocyst for this condition.

Over several years there were modifications and research undergone for the treatment of this condition involving wide bore needle aspiration, incision and drainage with drain placement, as if left untreated can lead to complications of infected seroma or perichondritis. Our study is to compare the outcomes of needle aspiration technique with drain placement techniques and to postulate the cost effectiveness and cosmetic outcomes [2].

Methods

This was a prospective comparative study done at a tertiary health care hospital. The duration of the study was 1 year and patients presented with pinna swelling were included in this study. Patients were explained about the nature of the condition and the outcome and were studied with informed consent. Out of 20 patients under random purposive method, 10 underwent wide bore needle aspiration technique and pressure dressing, rest 10 taken up for incision and drainage with drain in situ Table 1.

Aspiration with wide bore Needle

A wide bore needle or 16 gauge spinal needle with syringe was used in this technique .Under all aseptic precautions wide bore needle was introduced gently at the maximum prominence of the swelling and aspirated with syringe until the swelling reduced followed by tight pressure dressing was given.

Incision and Drainage with drain placement

Under all aseptic precautions, parts prepared and drapped. Local anaesthesia with 2% lignocaine infiltration was given post aurally to block the great auricular nerve and auriculotemporal nerve and also given around the incision site. Incision made with 15 number surgical blade at the most dependent site and fluid drained was sent for microbiological study. A small drain was kept either a rubber tube or corrugated drain or glove drain based on the availability and the drain is secured with sutures as shown in the image. Then pressure dressing was given and patient was asked to follow up till 7 days and drain is

removed subsequently after the purpose is served.

If patients of needle aspiration fails then they are taken for drainage and drain placement in subsequent visits.

Inclusion criteria

Patients coming to ENT Outpatient Department with painless boggy swelling of the pinna.

Patients willing for the study

Exclusion criteria

Patients having hematoma auris or perichondritis and patients not willing to take part in the study.

Results

Table 1: Techniques used for Seroma Treatment

	Widebore Needle Aspiration	**Incision & Drainage with Drain Insitu**
Male	9	8
Female	1	2
Total	10	10

Out of 20 patients in our study 10 underwent widebore needle aspiration and 10 patients underwent incision and drainage with drain placement Table 1.

Table 2: Distribution of Cases according to Age

Age group (years)	**Number of Cases in the group (n)**	**Percentage (%)**
15-20	0	0
21-25	0	0
26-30	2	10
31-35	**8**	**40**
36-40	**5**	**25**
41-45	2	10
46-50	2	10
51-55	1	5

Our patients were between the age group of 15–55 years. Most of the patients were in 3rd and 4th decade Table 2.

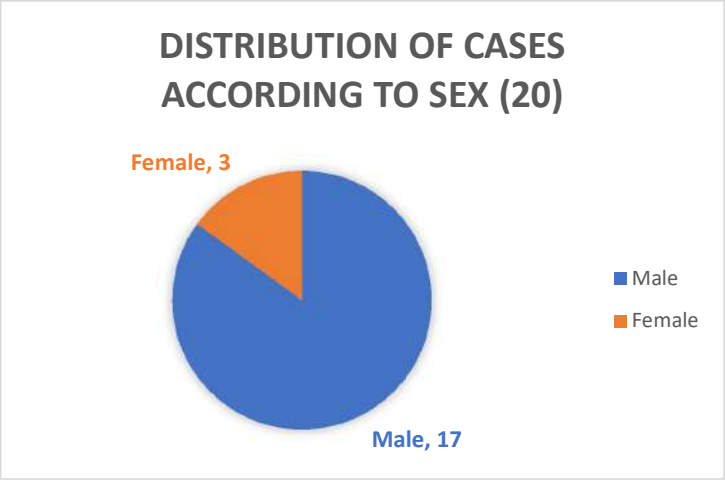


Figure 1. Distribution of Cases according to Sex

Out of 20 patients in our study, 17 were male and 3 females Figure 1.

Table 3: Recurrence in treated cases

Procedure	**Number of Cases primarily done**	**Recurrence (n-number of cases)**	**Percentage (%)**
Widebore Needle Aspiration	10	4	40
Incision & Drainage with Drain Insitu	10	0	0

The above tabulation shows 40% recurrence in our study in patients who underwent wide bore needle aspiration technique comparing with the drain placement technique Table 3.

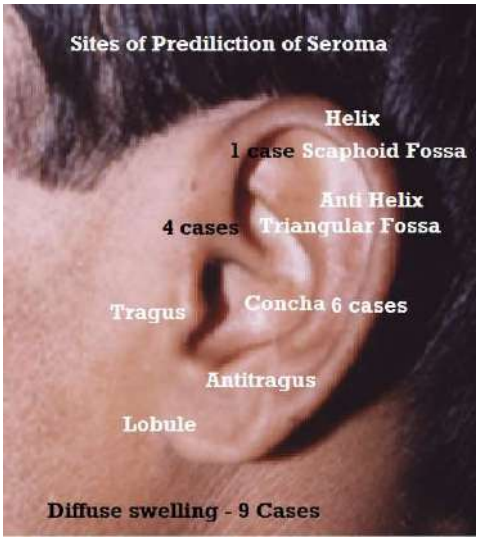


Figure 2. Distribution of seroma identified in our study

The image depicts the distribution of seroma cases in our study Figure 2.

Table 4. Materials used and their complications in Drainage Placement

Materials used for Drainage	**Number of Cases**	**Infected Cases**
Rubber drain	7	0
Corrugated drain	2	1
Glove drain	1	0

Table 4 shows the materials used in drain placement technique, Out of 10 cases underwent drain placement technique 1 case got infected with corrugated drain.

Table 5. Sequelae or Complications of the procedure performed

Sequelae\Complications	**Procedure**	
	Widebore Needle Aspiration (n-number of cases)	**Incision & Drainage with Drain Insitu (n-number of cases)**
Recurrence of swelling	4	0
Thickening of skin	0	**4 (Figure 2)**
Cosmetic deformity	0	0
Infection	3	1

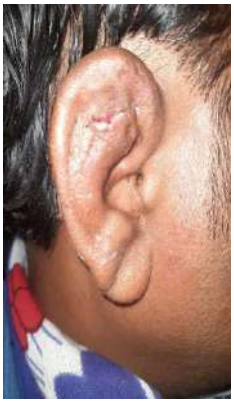


Figure 3. Showing post drain placement thickening of skin

Figure 4. Clinical pictures of Pinna Seroma with Site prediliction

Figure 5: Post Wide Bore Needle Aspiration showing Yellow sterile fluid

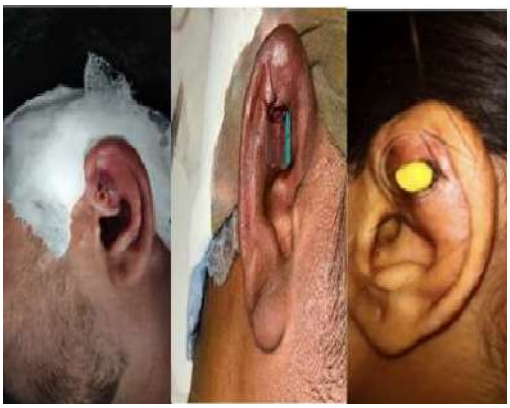


Figure 6. Post Drainage procedure pictures with drain tube insitu

Table 5 tabulates the sequelae or complications of the procedure performed in our study. Patients who underwent wide bore needle aspiration technique had 4 recurrences and 3 patients had secondary infection. Patients who underwent incision and drainage with drain placement technique had infection in 1 case and 4 cases had thickening of skin.

Discussion

Pseudocyst (seroma) of pinna is a condition where there occurs accumulation of serous fluid between the skin and cartilage either due to trivial trauma or degeneration. It is also called as pinna seroma\benign idiopathic chondromalacia\chondromalacia of pinna. Male gender are more commonly affected with this condition, postulating the use of helmets while driving or box fighting.

Hansen 1967 [3], has documented that pinna seroma was more commonly occurring in males and Shanmugam et al. (1985) [4] reported two cases of pinna seroma in females, which is comparable with our study results displayed in Figure 1.

Engel [5] cited that scaphoid fossa & triangular fossa in pinna are the most common sites of predilection which is comparable with our study showing almost 5 cases in these regions (Figures 2 and 4).

Choi et al. [6] postulated that it is due to degenerative process of the cartilage of the pinna resulting in the serous sterile fluid (oily yellow colour) Figure 5 [7] in the cavity and also added that cavity was filled with granulation tissue rather than epithelium and coined the name “Pseudocyst”.

Engel witnessed that wide bore aspiration of the swelling with pressure dressing had recurrence of the swelling as shown in the Table 3, whereas Zhu et al. [8] did incision and drainage with drain placement and showed good results (Table 4 and Figure 6) [9].

In our prospective study, patients were kept under follow up for a period of 6 months to watch out for sequelae of the disease and procedure done as shown in Table 5.

Conclusion

There are different modalities of treatment for pinna seroma concerned with the aim of draining the contents of the swelling and preventing recurrence. Our study showed that the incision and drainage with drain placement method could be performed in pinna seroma cases with good results.

Conflicts of interest

The authors declares that they do not have conflict of interest.

References

1. Wright, D. Diseases of External ear In Scott-Browns Otolaryngology 3rd vol. 6th edition (Kerr, A., Booth, J.B., eds), Buttworth & C.O., (Publishers) Ltd., pp 4, 1996.
2. Bhandary, S and Mannil, T. A comparative study in the management of auricular pseudocysts. Indian journal of otolaryngology and head and neck surgery: official publication of the Association of Otolaryngologists of India. (2000); 52: 246–50. DOI: 10.1007/BF03006193.
3. Hansen J.E. Pseudocysts of the Auricle in Caucasians Archives of Otolaryngology 1967; 85: 35–36.
4. Shanmugham, M.S. Pseudocyst of the auricle. Journal of Laryngology and Otiology 1985; 99: 701–703.
5. Engel D. Pseudocyst of the auricle in Chinese. Arch Otolaryngol. 1966; 83: 197–202.
6. Choi S, Lam KH and Chan KW et al. Endochondral pseudocyst of the auricle in Chinese. Arch Otolaryngol. 1984; 110(12): 792–6.
7. Cohen PR and Grossman ME. Pseudocyst of the auricle : case report and world literature review. Archives of Otolaryngology Head and Neck Surgery 1990; 116: 1202–1204.
8. Zhu LX and Wang XY. New technique for treating pseudocyst of the auricle. J Laryngol Otol. 1990; 104(1): 31–2.
9. Saunders MW, Jones NS and Balsitis M. Bilateral Auricular Pseudocyst: A case report and discussion. Journal of Laryngology and Otology 1993; 7: 39–41.

National Board of Examination - Journal of Medical Sciences

Volume 1, Issue 3, Pages 171–180, March 2023

DOI 10.61770/NBEJMS.2023.v01.i03.007

ORIGINAL ARTICLE

An analytical cross-sectional study on the determinants of nutritional anemia among children aged 1 to 5 years from Muzaffarnagar, India

Shivam Yadav[1,*], Manvi Agrawal[2], Renu Yadav[1], Manish Agrawal[1], Sangita Singhal[1] and Shekhar Sharma[1]

[1]*Department of Pediatrics, Muzaffarnagar Medical College, Muzaffarnagar, India*

[2]*Microsoft, Bengaluru, India*

Accepted: 25-February-2023 / Published Online: 01-March-2023

Abstract

Background: Nutritional anemia, one of the common causes of anemia, may result from the deficiency of a number of micronutrients. The present study was conducted to assess the prevalence of nutritional anemia and the clinico-haematological profile of anemia among the hospitalized children aged 1 to 5 years.

Materials and Methods: A cross sectional study was conducted among 250 anemic children between age one and five years attending the tertiary care hospital at Northern India. An interviewer administered questionnaire was used to obtain the data. Peripheral blood samples were used to assess the hematological parameters.

Results: The prevalence of nutritional anemia among the anemic 1-5 years old children was 27.6%, in which Iron deficiency anemia (IDA) prevalence was 21.2%. Vitamin B12 deficiency was found among 8% of the anemic children and folic acid deficiency was prevalent among the 1.6% of the cases. The mean hemoglobin levels were significantly lower in among the nutritional anemia children (8.75 g/dl).

Conclusion: Overall, the proportion of nutritional anemia among children aged one to five years is significant in Northern India, with IDA being the most common nutritional deficiency anemia.

Keywords: nutritional anemia; iron deficiency anemia; child; prevalence; India

*Corresponding author: Shivam Yadav
Email: drsky.paeds@gmail.com

Introduction

Despite the fact that anemia is largely preventable and easily curable, it remains a widespread health concern, especially in developing countries like India. In spite of economic prosperity and preventative measures, it remains a serious public health problem and a major reason for death and morbidity in children. It has been estimated that, globally 1.8 billion people are anemic, with children below 10 years of age bearing major brunt of this problem [1]. Anemia is thought to affect roughly 20.0% of children under the age of five in industrialised nations and 39.0% of children in non-industrialized nations [2]. Earlier estimates had reported that in developing nations, anemia affects up to 51.0% of children aged 0 to 4 and 46.0% of children aged 5 to 12 years [3,4]. Globally, the World Health Organization (WHO) reported the highest anemia prevalence (42%) among the children who are below the age of five years [5]. More specifically, children in the age between 6 and 59 months had an anemia prevalence of 39.8%, which translated to 269 million children in terms of absolute numbers [6]. Indian scenario is worse than the global picture with regards to the anemia. The National Family Health Survey of India in its latest round of results (5^{th} round), reported a 67.1% prevalence of anemia among the children between the age group 6 months and 59 months [7]. The most prevalent morbidity, anemia, has a negative impact on the health, productivity, and economics of the whole country [8].

Children's anemia is different from adult anemia since it usually manifests earlier and worsens at a rapid pace. Children's growth, development, well-being, and academic achievement are all profoundly impacted by anemia. Children's appetites are affected, which has an adverse effect on nutrition, and a vicious cycle is set in motion, making the issue worse. Children who are hospitalised often have co-morbid conditions, which may lengthen hospital stays, increase the risk of complications, and necessitate the need for blood transfusions [9].

Nutritional anemia, one of the common causes of anemia, may result from the deficiency of a number of micronutrients. The phrase "nutritional anemia" refers to any clinical disorders in which a nutrient shortage causes the blood haemoglobin concentration to fall to an abnormally low level. Iron, folic acid, and vitamin B12 are the principal nutrients necessary for the formation of haemoglobin. The most prevalent yet avoidable dietary deficit especially in children is the major cause for this morbidity. In terms of global public health, lack of iron is the primary cause of nutrition related anemia. Folic acid insufficiency is less common and usually present in conjunction with iron deficiency. Lack of vitamin B12 is relatively rare [8]. The majority of instances of anemia are caused by iron deficiency and proceed gradually. Iron deficiency anemia affects 30.0% of the world's population, according to the prevalence of anemia [10], with an annual incidence of 4-5 million cases [11].

The overall increased morbidity in children may be attributed to nutritional anemia, which can cause a number of physical and mental diseases. Because the anemic child is susceptible to infections and may fall into the vicious cycle of malnutrition-infection-malnutrition, it is a dangerous disorder in the paediatric age range. Additionally, it may have an impact on the child's general mental and motor development [2]. The false belief that there are no feasible and effective therapies has often limited efforts and projects to prevent and manage anemia. Nutritional anemia is easily preventable and inexpensive to cure.

Population-based data on the prevalence of anemia among the children below five years are available for India. However, data on the hematological attributes and the associated factors in hospitalized children are limited, especially in the current settings of Northern India. Hence, we conducted the following study to assess the prevalence of nutritional anemia and their clinico-haematological profile among the hospitalized anemic children aged 1 to 5 years.

Materials and Methods

Study design: Hospital based cross sectional study

Study Period: January 2021 to July 2022

Study Population: Children belonging to the ages between one and five years who were admitted to the inpatient department of a pediatric ward at Muzaffarnagar medical college, and whose hemoglobin levels were less than or equal to 11 gm/dl were included. Children with any chronic disease or had been transfused with blood in the last 3 months or received any hematinics in last three months were not included.

Sample Size: According to the prevalence of nutritional anemia among the children aged 1-4 years as 68.9% from a survey [12], taking a relative error of 10%, at 95% confidence interval, a minimum sample size of 228 was calculated. Adding 10% non-completion rate/missing data, a sample size of 251 anemia children was calculated.

Sampling technique: Consecutive sampling with complete enumeration of all eligible children till the sample size was achieved.

The major outcomes are the prevalence of nutritional anemia, hematological profile of nutrition anemia children and the determinants of nutritional anemia.

Data collection

After obtaining the parent's or the child's legally recognised representative's signed informed consent, anemic children in inpatient departments who satisfy the inclusion criteria were inducted into the study. An interviewer administered bilingual (English & Hindi) questionnaire was used to obtain the data on the socio-demography, feeding practices and the infection history of children, from the attendants who brought the child. Additionally performed were a thorough history, examination of the child, anthropometry, as well as a systemic examination according to a predesigned proforma. Age of the child was recorded in completed months. Peripheral blood samples were drawn under aseptic conditions and submitted for investigation of the complete blood count, peripheral smear, serum iron indices, folic acid, serum vitamin B12 levels and other hematological indices. Nutritional anemia is determined based on the serum levels of vitamin B12 (less than 203 pg/ml), folate (less than 4 ng/ml) and ferritin levels (less than 12 mcg/L).

Data analysis

Data was entered in MS excel. Analysis was conducted in SPSS 26.0. Categorical variables were expressed in frequencies and proportions. Normality of Continuous variables were tested (Kolmogorov Smirnov test) and data was assessed to be not normally distributed. Mann-Whitney test was applied to test the association between continuous variables and nutritional anemia status. To investigate the relationship between categorical variables, the chi-square test was applied. Spearman correlation was used to test the association between serum ferritin, vitamin B12, folic acid levels and the hematological indices. Statistical significance was taken as a p value below 0.05.

Ethical review

The study didn't include any experimentation. Informed consent was gained after fully explaining the study purpose and process to the child attendants (parents/guardians). No monetary or personal benefits from commercial bodies were provided to anybody involved in the study. Ethics approval for the study was taken from the institution ethics committee before the start of the research. Confidentiality of the data was maintained.

Results & Discussion

Anemia is still a major public health issue on a worldwide scale. Nutritional anemia is a

major cause of morbidity and economic burden across the globe, especially in the lower- and middle-income countries. Epidemiological characteristics and determinants of the nutritional anemia will enable the policy makers in better formulation of the strategies to manage it. The present study was undertaken in a tertiary care institutional settings in Northern India to evaluate the burden, clinical and hematological features of the nutritional anemia among the children between one and five years of age. The total number of anemic children who were enrolled and completed the study was 250 (response rate of 99.60%).

The prevalence of nutritional anemia among the anemic 1–5 years old children was 27.6%, with Iron deficiency anemia (IDA) accounting for three fourth of the nutritional anemia cases (21.2%). This is similar to the prevalence of IDA reported from Ethiopia (25%) among children aged between two and five years [13]. In contrast, Levin et al reported lower prevalence of iron deficiency anemia among their children (5.8%) [14]. Although iron deficiency anemia affects people across the age group, children are one of the most vulnerable groups for this deficiency anemia [15].

The mean age of the nutritional and non-nutritional anemic children included in our study was 38.32 and 38.55 months, respectively. Among the children with nutritional anemia, there was similar proportion of males (50.7%) and females, while majority were in the age group of 48-60 months. The mean BMI of children with nutritional anemia was 13.77 kg/m^2. (Table 1).

Various hematological and micronutrients levels of the children with nutritional anemia are enumerated in Table 1. The mean ferritin and iron level among the nutritional anemia children was 13.88 ug/L and 34.71 ug/dl, respectively. Levin et al reported a lower ferritin levels of 6.58 ng/dl among the children between 18 and 36 months with iron deficiency anemia in their study from Israel [14]. Children with nutritional anemia in the index study had a significantly lower PCV, MCV, MCH, platelet count, transferrin saturation, serum iron and ferritin, while they had significantly higher RDW and TIBC. This is in line with findings from the past research which had reported a similar relationship of these indices with the iron deficiency anemia.[16] Levin et al reported significantly lower ferritin among the iron deficient anemic children than the other anemia [14]. The mean hemoglobin levels were significantly lower in among the nutritional anemia children (8.75 g/dl) in the present study, indicating the higher severity of anemia due to nutritional deficiency. (Table 1)

While Vitamin B12 deficiency was found among 8% of the anemic children, folic acid deficiency was prevalent among the 1.6% of the cases. This distribution of megaloblastic anemia is in line with the findings of previous study from India, where Vitamin B12 was relatively more prevalent than folate deficiency [17]. In contrast, Umasanker et al reported much higher prevalence of Vitamin B12 deficiency (64.8%) among the clinically determined anemic children [18]. The mean vitamin B12 and Folic acid levels were 452.03 pg/ml and 19.69 ng/ml, among the children with nutritional anemia in our study. Umasanker et al reported lower Vitamin B12 levels than our study (189 pmol/L) [18]. Tetrahydrofolate, an essential component of DNA synthesis, can only be produced by the body when vitamin B12 is present [19]. If left untreated, vitamin B12 insufficiency in children is a serious, treatable public health issue that might have long-term neurological effects [18,20]. The dietary practices and history of these children would have given an explanatory picture, since Vitamin B12 deficiency is associated with decreased intake of animal diet. Concurrent deficiency of Iron as well as Vitamin B12 was diagnosed among 2.8% of the children in the index study. Such a combined deficiency has been reported to present as delayed puberty in the later stages of child [19].

Table 1: Association between the nutritional anemia and the demographic, clinical and hematological parameters (N=250)

Variable	**Nutritional Anemia**				p value*
	Yes (69)		**No (181)**		
	Mean	**SD**	**Mean**	**SD**	
Age (months)	38.32	16.46	38.55	15.02	0.658
Height (cm)	92.83	11.47	93.07	9.58	0.872
Weight (kg)	11.92	2.99	11.71	2.45	0.721
BMI	13.77	2.14	14.25	10.06	0.390
Hb (g/dl)	8.75	1.32	9.55	1.13	**<0.001**
TLC (cells/cu.mm)	11094.20	4592.09	10295.03	4557.49	0.219
RBC(millions/cu.mm)	4.52	0.76	4.42	0.51	0.052
PCV (%)	29.16	8.55	31.42	4.48	**<0.001**
MCV (fL)	64.23	9.95	69.05	15.32	**<0.001**
MCH (pg)	20.56	5.84	21.98	3.36	**0.002**
MCHC (%)	30.59	2.32	33.01	20.98	0.462
RDW (%)	16.32	3.53	14.93	3.49	**0.001**
Platelet count(cells/cu.mm)	3.83	1.61	4.05	6.53	**0.004**
Reticulocyte count (%)	0.91	0.84	0.82	0.47	0.729
TIBC (umol/L)	407.52	92.49	321.01	91.86	**<0.001**
Transferrin saturation(%)	8.42	4.97	14.28	11.60	**<0.001**
S. Transferrin (mg/dl)	442.17	86.91	369.09	80.34	**<0.001**
S.Iron (ug/dl)	34.71	16.46	48.07	27.45	**<0.001**
S.Ferritin (ug/L)	13.88	23.23	103.22	208.18	**<0.001**
Vitamin B12(pg/ml)	452.03	259.02	464.64	159.44	0.230
Folic acid (ng/ml)	19.69	30.65	29.29	124.27	0.871

*Mann-Whitney test

With regards to the feeding practices, majority of the children with nutritional anemia did not have (>80%) exclusive breast feeding. There was no significant association between demographic and infant feeding practices of the children (Table 2) Prolonged breastfeeding has shown to have a negative impact on the anemia in children less than 5 years age [21]. However, neither the exclusive breast-feeding nor the timing of initiation of the complimentary feeding had a significant association with the nutritional anemia in the present study. In contrast, late weaning has been associated with increased risk of iron deficiency anemia among other causes, since this directly affects the iron stores of the baby [16,22]. Maternal diet has shown to impact the Vitamin B12 levels especially in the children less than 24 months of age [23].

Table 2: Association between the nutritional anemia and the probable etiological factors (N=250)

Factors	Nutritional Anemia				p value*
	Yes (69)		No (181)		
	Frequency	%	Frequency	%	
Sex					
Male	35	50.7	108	59.7	0.201
Female	34	49.3	73	40.3	
Age (months)					
12-24 months	18	26.1	33	18.2	0.544
12-36 months	16	23.2	52	28.7	
36-48 months	12	17.4	34	18.8	
48-60 months	23	33.3	63	34.3	
Exclusive breast feeding					
0-1 Month	5	7.2	13	7.2	0.793
1-4 Month	18	26.1	55	30.4	
4-6 Month	33	47.8	90	49.7	
6-12 Month	9	13	16	8.8	
>12 Month	4	5.8	6	3.3	
Introduction of complimentary feeding					
< 6 Months	3	4.3	8	4.4	0.155
6-10 Months	15	21.7	63	34.8	
10-12 Months	33	47.8	80	44.2	
>12 Months	18	26.1	30	16.6	
Introduction of artificial feeding					
0-1 Month	1	1.4	7	3.9	0.123
1-4 Month	24	34.8	57	31.5	
4-6 Month	12	17.4	53	29.3	
6-12 Month	29	42	62	34.3	
>12 Month	3	4.3	2	1.1	

*Chi-square test

Significantly higher proportion of children without nutritional anemia presented with lethargy (Table 3). In terms of the severity, significantly higher proportion of the children with nutritional anemia had moderate anemia (75.4%) while majority of the non-nutritional anemia cases were mild (50.8%). Nutritional anemia children had a significantly higher mircocytic hypochromic picture in the peripheral smear (55.1%), which can be attributed to the high Iron deficiency anemia in the children [24]. Although 9.6% of the children in the index study had Vitamin B12 or folic acid deficiency, megaloblastic picture or dimorphic presentation was not observed in the peripheral smear.

Table 3: Association between the nutritional anemia and manifestations in the study participants (N=250)

Manifestations	**Nutritional Anemia**				p value*
	Yes (69)		**No (181)**		
	Frequency	**%**	**Frequency**	**%**	
Presenting symptoms					
Pale Skin	50	72.5	110	60.8	0.085
Irritability	20	29	59	32.6	0.583
Lethargy	13	18.8	59	32.6	**0.032**
Easy Fatigue	14	20.3	51	28.2	0.204
Poor Appetite	17	24.6	60	33.1	0.193
Abnormal Rapid Breathing	1	1.4	9	5	0.204
Other Symptoms					
Pallor	69	100	181	100	-
Icterus	0	0	1	0.6	0.536
Lymphadenopathy	0	0	1	0.6	0.536
Edema	1	1.4	0	0	0.105
Clubbing	0	0	1	0.6	0.536
Cyanosis	1	1.4	0	0	0.105
Koilonychia	2	2.9	7	3.9	0.713
Glossitis	1	1.4	1	0.6	0.477
Chelitis	6	8.7	18	9.9	0.764
Cardiac murmur	3	4.3	0	0	**0.005**
Other factors					
PICA	14	20.3	35	19.3	0.865
Passage Of Worms	14	20.3	50	27.6	0.235
Behavioural Problems	12	17.4	47	26	0.153
Frequent Infections	5	7.2	6	3.3	0.175
H/O Major Illness	1	1.4	0	0	0.105
Severity of anemia					
Mild	14	20.3	92	50.8	**<0.001**
Moderate	52	75.4	81	44.8	
Severe	3	4.3	8	4.4	
Peripheral smear					
Normocytic and hypochromic	5	7.2	19	10.5	**0.003**
Microcytic and hypochromic	38	55.1	57	31.5	
Normocytic and normochromic	26	37.7	105	58	

*Chi-square test

In the present study, there was mild but significant correlation between the hemoglobin, RBC count, PCV, MCV, MCH and the serum ferritin. There was mild but significant correlation between the RBC count, MCH, MCHC and the serum Vitamin B12. There was mild but significant correlation between the RDW, MCHC and the serum folic acid. (Table 4)

Table 4: Correlation between the Hematological indices and the micro-nutrient levels

Hematological indices	Serum ferritin		Vitamin B12		Folic Acid	
	correlation	p value*	correlation	p value*	correlation	p value*
Hb	0.246	**<0.001**	-0.107	0.092	-0.070	0.272
RBCs	-0.149	**0.018**	0.238	**<0.001**	-0.049	0.444
PCV	0.204	**0.001**	0.019	0.767	-0.121	0.056
MCV	0.239	**<0.001**	-0.087	0.170	-0.095	0.133
MCH	0.179	**0.005**	-0.257	**<0.001**	-0.077	0.225
MCHC	0.120	0.057	-0.284	**<0.001**	0.148	**0.019**
RDW	-0.104	0.102	0.006	0.930	0.167	**0.008**
Reticulocyte count	-0.038	0.546	0.046	0.467	0.068	0.288

*Spearman correlation

Strengths & Limitations

The present study was undertaken with adequate power based on statistically calculated sample size. The hematological parameters were assessed in the accredited laboratories improving the validity. Data on the history and symptoms were collected by the single investigator, thus avoiding inter-rater bias. However, the index study is not devoid of limitations. The cross-sectional design of the study limits the confirmation of the association between the potential factors and the nutritional anemia. Selection bias may be present owing to inclusion of children who were hospitalized, rather than from the community, which limits the generalizability of the findings.

Conclusion

Overall, the proportion of nutritional anemia among children from one to five years is significant in Northern India. Prevalence of Iron deficiency anemia was 21.2% among the under five anemic children. Vitamin B12 and folate deficiency also contributes towards nutritional anemia. National health programs such as Anemia Mukt Bharat needs to be leveraged to address the nutritional causes of the anemia, as it is completely preventable as well as treatable. The severity of the anemia was also high among the children with nutritional anemia. Further, analytical studies to confirm the association of the clinical and hematological factors with nutritional anemia needs to be conducted in future. Community based studies, with dietary pattern need to be conducted to verify and improve the generalisability of our findings.

Conflicts of interest

The authors declares that they do not have conflict of interest.

Funding

No funding was received for conducting this study.

References

1. Safiri S, Kolahi A-A, Noori M, Nejadghaderi SA, Karamzad N, Bragazzi NL, et al. Burden of anemia and its underlying causes in 204 countries and territories, 1990–2019: results from the Global Burden of Disease Study 2019. J Hematol Oncol. 2021;14(1):185. https://doi.org/10.1186/s13045-021-01202-2
2. Keikhaei B, Zandian K, Ghasemi A, Tabibi R. Iron-deficiency anemia among children in southwest Iran. Food Nutr Bull. 2007 Dec;28(4):406–11.
3. Garder B. Anemias of Inadequate Production. In: Kliegman R, Behrman RE, Jensen HB, Stanton BF, editors. Nelson Textbook of Pediatrics. Philadelphia: W.B. Saunders; 2008. p. 2011–4.
4. Madoori S, C. R, Valugula S, G. S, Kotla S. Clinico hematological profile and outcome of anemia in children at tertiary care hospital, Karimnagar, Telangana, India. Int J Res Med Sci. 2015;3(12):3567–71. https://www.msjonline.org/index.php/ijrms/article/view/1959
5. World Health Orginazation. Anaemia.: https://www.who.int/health-topics/anaemia#tab=tab_1
6. World Health Orginazation. Anaemia in women and children. https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children
7. Jana A. Anaemia in women, children aggravated in 2019: NFHS-5. Available from: https://www.downtoearth.org.in/blog/health/anaemia-in-women-children-aggravated-in-2019-nfhs-5-74799
8. Kotecha P V. Nutritional anemia in young children with focus on Asia and India. Indian J community Med Off Publ Indian Assoc Prev Soc Med. 2011 Jan;36(1):8–16.
9. Ramawat D, Jain N. Clinicohematological Profile of Anemia in Children – A Retrospective Descriptive Study. Sch J Appl Med Sci. 2020 Oct 15;8:2266–70.
10. Cusick SE, Mei Z, Freedman DS, Looker AC, Ogden CL, Gunter E, et al. Unexplained decline in the prevalence of anemia among US children and women between 1988-1994 and 1999-2002. Am J Clin Nutr. 2008 Dec;88(6):1611–7.
11. Bathla S, Kannan E. Introduction BT - Agro and Food Processing Industry in India: Inter-sectoral Linkages, Employment, Productivity and Competitiveness. In: Bathla S, Kannan E, editors. Singapore: Springer Singapore; 2021. p. 1–14. https://doi.org/10.1007/978-981-15-9468-7_1
12. Chandra J, Dewan P, Kumar P, Mahajan A, Singh P, Dhingra B, et al. Diagnosis, Treatment and Prevention of Nutritional Anemia in Children: Recommendations of the Joint Committee of Pediatric Hematology-Oncology Chapter and Pediatric and Adolescent Nutrition Society of the Indian Academy of Pediatrics. Indian Pediatr. 2022;59(10):782–801.
13. Orsango AZ, Habtu W, Lejisa T, Loha E, Lindtjørn B, Engebretsen IMS. Iron deficiency anemia among children aged 2–5 years in southern Ethiopia: A community-based cross-sectional study. Peer J. 2021;9.
14. Levin C, Harpaz S, Muklashi I, Lumelsky N, Komisarchik I, Katzap I, et al. Iron deficiency and iron-deficiency anemia in toddlers ages 18 to 36 months: a prospective study. J Pediatr Hematol Oncol. 2016;38(3):205–9.
15. Natekar P, Deshmukh C, Limaye D, Ramanathan V, Pawar A. A micro review of a nutritional public health challenge: Iron deficiency anemia in India. Clin Epidemiol Glob Heal 2022;14:100992. https://www.sciencedirect.com/science/article/pii/S2213398422000331
16. Moscheo C, Licciardello M, Samperi P, La

Spina M, Di Cataldo A, Russo G. New Insights into Iron Deficiency Anemia in Children: A Practical Review. Metabolites 2022;12(4).

17. Chandra J, Jain V, Narayan S, Sharma S, Singh V, Kapoor AK, et al. Folate and cobalamin deficiency in megaloblastic anemia in children. Indian Pediatr. 2002 May;39(5):453–7.
18. Umasanker S, Bhakat R, Mehta S, Rathaur VK, Verma PK, Bhat NK, et al. Vitamin B12 deficiency in children from Northern India: Time to reconsider nutritional handicaps. J Fam Med Prim Care 2020;9(9):4985.
19. Song SM, Bae KW, Yoon H-S, Im HJ, Seo J-J. A case of anemia caused by combined vitamin B12 and iron deficiency manifesting as short stature and delayed puberty. Korean J Pediatr. 2010 May;53(5):661–5.
20. Kapil U, Sareen N. Prevalence of ferritin, folate and vitamin B12 deficiencies amongst children in 5-18 years of age in Delhi. Indian J Pediatr. 2014 Mar;81(3):312.
21. Khan JR, Awan N, Misu F. Determinants of anemia among 6–59 months aged children in Bangladesh: evidence from nationally representative data. BMC Pediatr 2016;16(1):3. https://doi.org/10.1186/s12887-015-0536-z
22. Mantadakis E, Chatzimichael E, Zikidou P. Iron Deficiency Anemia in Children Residing in High and Low-Income Countries: Risk Factors, Prevention, Diagnosis and Therapy. Mediterr J Hematol Infect Dis 2020;12(1).
23. Cetinkaya F, Yildirmak Y, Kutluk G, Erdem E. Nutritional vitamin B12 deficiency in hospitalized young children. Pediatr Hematol Oncol. 2007;24(1):15–21.
24. Chaudhry HS, Kasarla MR. Microcytic hypochromic anemia. Starpearls. 2017. https://www.ncbi.nlm.nih.gov/books/NBK470252/

National Board of Examinations - Journal of Medical Sciences
Volume 1, Issue 3, Pages 181–184, March 2023
DOI 10.61770/NBEJMS.2023.v01.i03.008

CASE REPORT

Right atrial thrombus successfully treated with Heparin

Amit Kumar[1,*], Sudhakar A[2], Ramakrishna Reddy[3] and Ganpat Jha[4]

[1]*Consultant Neonatologist, Sri Krishna Children Hospital, Warangal, India*
[2]*Prof of Pediatrics Kakatiya Medical College Warangal, India*
[3]*Consultant, Cardiologist Sreeram Heart Centre Warangal, India*
[4]*Pediatric Intensivist, Sri Krishna Children Hospital, Warangal, India*

Accepted: 18-February-2023 / Published Online: 01-March-2023

Abstract
Background: - Thrombi are common complication of long line like umbilical venous catheter or peripherally inserted central catheter (PICC) mainly in extreme and very preterm baby but there is no well-formed protocol for its treatment in pediatrics age group especially in Neonates. There are still very less cases are reported.
Case Presentation: - Male DCDA twin 2 with birth weight of 750 gram had secondary deterioration on day 21 of life with recurrent apnea poor perfusion and increased oxygen requirement. Echo showed a large thrombus in right atrium which was successfully treated with infusion of unfractionated Heparin followed by subcutaneous low molecular weight Heparin.
Conclusion: - Right atrial thrombus is a common complication of central line mainly in preterm baby and Heparin gives good result without any complications if baby is hemodynamically stable and urgent thrombolysis in not required.

Keywords: Thrombus, PICC line, thrombocytopenia, rTPA, LMWH

*Corresponding author: Amit Kumar
Email: amit.gmch14@gmail.com

List of abbreviations

UVC-umbilical venous catheter
PICC- peripherally inserted central catheter
DCDA- Dichorionic Diamniotic
ICSI- Intracytoplasmic sperm Injection
PROM- Prolonged rupture of membrane
NEC- Necrotizing Enterocolitis
IVH- Intraventricular Hemorrhage
rTPA- Recombinant Tissue Plasminogen Activator
LMWH- Low Molecular weight Heparin

Introduction

Thrombi are common complication of long line like umbilical venous catheter or peripherally inserted central catheter (PICC) mainly in extreme and very preterm baby. Option available for treatment of thrombus is ranges from no treatment to use of heparin and thrombolytic agent like recombinant tissue plasminogen activator. Also, there is well formed protocol guideline for thrombi in adult but for neonates still there is no well-formed guideline for treatment of thrombus due to life threatening bleeding complication of heparin and recombinant tissue plasminogen activator. Apart from this there is only few cases are reported and there is very much discrepancy in treatment in neonates. Here we are reporting our case of right atrial thrombus in 28 weaker 750-gram baby which was successfully treated with heparin without any bleeding complications.

Presentation

A male second DCDA twin with 28 wks gestation with birth weight of 750 gram, Small for gestation born to 28 years old primi mother conceived by ICSI conception. This pregnancy was complicated by PIH and abnormal doppler. There is no history of early infantile deaths, early-onset stroke, or coronary heart disease in any of the family members.

Baby was delivered by emergency LSCS in view of PROM and draining PV. Baby had normal transition and did not require any resuscitation at birth. Baby had mild respiratory distress with SAS score of 2/10 for which supported by HFNC for 7 days of life and chest Xray was suggestive of transient tachypnea of newborn.

Umbilical line was established on day one and total parenteral nutrition was given and after 10 days umbilical line was removed and PICC line was inserted, and position was confirmed by Xray.

On day 12 baby had recurrent apnea and poor perfusion with thrombocytopenia and hyponatremia and clinical picture was suggest of NEC, managed conservatively with antibiotics, ionotropic support and platelet was transfused. Baby was improved clinically over period and feed was restarted.

Till day 12 screening Neurosonogram showed grade one IVH and Echo showed small PFO with normal four chamber and was not suggestive of any intracardiac mass.

For thrombocytopenia three times platelets were transfused, blood culture grown Candida tropicalis for which inj fluconazole was given but still platelet count was not improving beyond 40000 per cumm. On day 21 again baby had recurrent desaturation with poor perfusion and baby became pale for which baby was put on respiratory support with HFNC and inotropes (inj Dobutamine) was started for poor perfusion and normal non-invasive blood pressure was normal 53/43mmHg and mean was 46 mmHg. Blood test showed drop in platelet counts to 20000/cumm, hemoglobin 8g/dl with other parameter like sodium, calcium and LFT were within normal range with normal blood gas. Neurosonogram showed non progressive grade one IVH.

Echocardiography showed large right atrial thrombus of size 10 mm × 6 mm arising from intra-atrial septum and obstructing Tricuspid valve (fig.) but flow was present.

Management

Clinically baby had desaturation with poor perfusion, started on HFNC support with 30% fio2 and Dobutamine infusion. Negative CRP and normal chest x-ray with normal lungs finding had ruled out pneumonia and other infection inspite of thrombocytopenia (platelet count 20000/cumm). In view of large right atrial thrombus with symptomatic baby after discussing with cardiologist unfractionated Heparin was started as continuous infusion at the dose of 28 units/kg per hour inspite of low platelet count because. We thought thrombocytopenia may be due to over consumption because it was not improving even after transfusing platelets and giving appropriate antibiotics for fungal infection. We have not given Tissue plasminogen activator as baby was hemodynamically stable and there may be more chance of bleeding due to tissue

plasminogen activator. PT APTT and INR was monitored, anti-factor Xa level could not be done due to logistic reason. PT APTT was slightly on higher range after 48 hrs of Heparin infusion but there was not any bleeding manifestation was noted in the baby. After 48 hours of Heparin infusion, Platelet counts were improved, and size of thrombus was reduced. After 3 days of unfractionated Heparin infusion, it was switched over to Low Molecular weight Heparin at the rate of 2 mg/kg per dose Subcutaneously 12th hrly. Gradually after 10 days of Enoxaparin, thrombus was dissolved completely, Enoxaparin was given for 3 wks and stopped.

Discussion

Atrial thrombus is a common complication of malposition of long line like UVC or PICC in neonates but can happen in normally positioned long line due to difference in neonatal coagulation system from those of children and adults, with a higher level of factor VIII and von Willebrand factor activity and low levels of factors II, VII, IX, X, XI, and XII (). Incidence is equal in Term or Preterm and Male or Female baby, but Prematurity and Intravenous catheters are common risk factors or thrombus formation as intravenous catheter act as nidus for Platelet & Fibrin accumulation [2,3,5].

Guideline for the use of thrombolytic agents in adult is well established but still there is no proper guideline in Pediatric patient and especially in Newborn (5). Treatment option of right atrial thrombus is consits of no treatment, Heparinization, thrombolysis with thrombolytic agent like recombinant Tissue Plasminogen Activator followed by low molecular weight heparin infusion or surgical removal. Various reported cases from Murki et al. and Dewals et al. had used rTPA for acute lysis of thrombus in hemodynamically unstable baby or crashing baby without any complication but one case from Alicia sheen et al had used Heparin infusion for relatively stable baby with atrial thrombus with significant reduction in size of thrombus [6,7]. Iin our case we had treated the atrial thrombus successfully with Heparin and rTPA was not used as baby was hemodynamically stable and we had found very good result with Heparin without any complication.

Conclusion

Acute or subacute deterioration with Apnea, Desaturation Persistent Thrombocytopenia with normal sepsis marker without lung finding in preterm baby with risk factor like long line like UVC or PICC line, we must keep the chance of thrombus in our mind. rTPA should be used for hemodynamically unstable baby and Heparin gives good result without any complications baby is hemodynamically stable and urgent thrombolysis in not required.

Conflicts of interest

The authors declares that they do not have conflict of interest.

Funding

No funding was received for conducting this study

References

1. Saxon House MA, Manco-Johnson MJ. The evaluation and management of neonatal coagulation disorders. Semin Perinatol. 2009; 33(1): 52–65.
2. van Elteren HA, Veldt HS, Te Pas AB, et al. Management and outcome in 32 neonates with thrombotic events. Int J Pediatr.2011; 2011: 217564.
3. Turebylu R, Salis R, Erbe R, Martin D, Lakshminrusimha S, Ryan RM. Genetic prothrombotic mutations are common in neonates but are not associated with umbilical catheter-associated thrombosis.J Perinatol. 2007; 27(8): 490–495.
4. uchs S, Pollak A, Gilon D. Central venous catheter mechanical irritation of the right atrial free wall: a cause for thrombus formation. Cardiology. 1999; 91(3): 169–172.
5. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, (9thedn), American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e737S-e801S.
6. Dewals W, Benatar A (2018) Life-threatening right atrial thrombus in a premature newborn successfully treated with recombinant tissue plasminogen activator. Clin Case Rep Rev 4: DOI: 10.15761/CCRR.1000392.
7. Rahul S G, Srinivas M. Newborn with acute-onset central cyanosis. Neo Reviews 2018; 19; e686.