September 2020

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E journal of Paediatrics

Issue.4

Vol.1

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Dr. P.V.Ramana Murthy M.S.FRCS (UK)
Managing Director, Chief Surgical Gastroenterologist

Prakasam Road,Govenorpet.	Heart & Brain Institute, Suryaraopet	Bhavanipuram, Vijayawada.
On Call Paediatrician : 8466996310	On Call Paediatrician : 8466998754	On Call Paediatrician : 9603066888
Ph : 0866-2574757,2576757	Ph : 0866-2442333	Ph : 0866-2415757, 2414167

DEPARTMENT OF PAEDIATRICS, ANDHRA HOSPITALS, VIJAYAWADA
E-JOURNAL

VOLUME 01 ISSUE 04 SEPTEMBER 2020

Foreword

Greetings from the Andhra Hospitals!

For the past two decades, we are delivering excellence in terms of quality health care in the field of Paediatrics including Paediatric and Neonatal intensive care, Paediatric cardiac intensive care and other allied Paediatric sub-specialities.We take pride in introducing ECMO in pediatric specialty for the first time in the state of Andhra Pradesh. In this context, we convey our heartfelt thanks to you for your continued support and encouragement which played a pivotal role in our success.

As a token of our commitment to contribute to continuous medical education, we are introducing this monthly E-journal to showcase important clinical guidelines, recent advances in paediatric sub-specialties, interesting case reports, image quiz, OSCE scenarios etc, gathered from our patient database.

We hope this endeavor would prove to be useful to practicing paediatricians, intensivists, neonatologists and post-graduate students.

Please send your valuable feedback and suggestions to ***maramkp@gmail.com***.

Dr. P. V. Ramana Murthy M.S. FRCS (UK)

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Index

High-Flow Nasal Cannula Therapy in Paediatrics

Dr. Bhanu Prasad. D[1] Dr M. Krishna Prasad[2,]

[1,2] **PICU Consultant, Andhra Hospital**

Abstract

Heated Humidified High Flow Nasal Cannula (HHHFNC) devices deliver an adjustable mixture of heated and humidified oxygen and air at a variable flow rate. Over recent years HHHFNC devices have become a popular method of non-invasive respiratory support in infants and preterm neonates due to ease of use and being well tolerated by infants. Recent evidence suggests that HHHFNC therapy may reduce work of breathing and improve the efficiency of ventilation in newborn infants, possibly with clinically significant outcomes such as avoidance of the need for nCPAP and a reduced requirement for invasive ventilation. Despite its rapid adoption, there is relatively limited data about the exact mechanisms of action of HHHFNC. There is growing evidence of the feasibility of HHHFNC as an alternative to other forms of non-invasive ventilation in preterm infants. We review the mechanisms of action, and the supporting evidence in favour of using heated humidified high-flow nasal cannula therapy in newborn infants and older children.

Keywords High flow, nCPAP, Ventilation, preterm, nasal cannula

Introduction

Respiratory support plays a crucial role in the management of critically ill neonates. In light of evidence of injury to the lungs with mechanical ventilation, the use of non-invasive modes of ventilation (NIV) delivered through a nasal cannula is growing fast. Various modes of respiratory support through nasal cannulae, along with supportive evidence, are available including nasal continuous positive airways pressure (nCPAP), bi-level positive airways pressure (BiPAP), and nasal intermittent positive pressure ventilation (NIPPV). However, the use of bi-nasal prongs to deliver nCPAP/BiPAP/NIPPV is often cumbersome, requires a tight seal around nares, and can also result in trauma to the nasal septum and distortion of the nares.

Traditionally a simple nasal cannula (low flow nasal cannula) delivers unblended, non-heated, non-humidified oxygen at lower flow rates (<1 L/min). Any higher flow rates are poorly tolerated due to irritation and drying of nasal mucosa, and carry a risk of infection. In addition, there was a difficulty in delivering desired fractional inspired oxygen concentration (FiO_2) due to dilution by entrained room air. However, heating (to body temperature) and humidification (to >99% relative

humidity) of blended air and oxygen mixtures would avoid the above risks and complications. Delivery of flow rates which match or exceed the patient's inspiratory flow rate may enable delivery of desired FiO_2 by limiting mixing by room air. This is the principle of heated humidified high-flow nasal cannula (HHHFNC) therapy, which is increasingly being used across all parts of the globe, and has become established as a popular mode of respiratory support in neonatal, paediatric and adult critical care units. Despite its widespread use, the evidence in support of its efficacy and safety is not yet fully established. We review the physiological mechanism of action and the clinical evidence supporting the use of HHHFNC.

Description

Currently, there is a lack of agreement on what flow constitutes "high flow". Two Cochrane reviews (2011, 2016) defined it as flow rates above 1 L/min, although accumulating evidence shows that a minimum flow of more than 2 L/min is needed to witness the clinical benefit of modern HHHFNC devices. Commercially available HHHFNC devices consist of a closed system, whereby a blend of air and oxygen can be produced at variable gas flows. These gases are heated to near body temperature at 37^0 C, humidified (95-100% relative humidity) and delivered to the patient through a nasal cannula. Some models incorporate a pressure limiting valve (below 35 cm H_2O) as a safety feature. The range of flow rates in neonates (1-8 L/min) older children (upto 40 L/m), heating, and humidification methods vary according to manufacturer recommendations. Some devices have a proprietary semi-permeable membrane that separates inflowing gas from the heated water allowing only heated vapour to mix with the gas (Vapotherm™), while others allow for a common chamber between inflowing gas, heated water and vapour (Optiflow™). The various manufacturers have unique compatible nasal cannula sizes (to fit extreme preterm infants up to adults) and interfaces that fit their own humidifiers. Comparison studies of HHHFNC devices (Miller 2010) or humidification devices (Sadeghnia 2014) showed no significant differences in their efficacy or outcomes.

Mechanism of action

Numerous theories exist regarding the mechanism of action of HHHFNC and its proposed clinical benefits. Much of this evidence has stemmed from the results of various observational physiological studies involving HHHFNC devices in animals and adults. It is very likely that several of these mechanisms are at work during HHHFNC therapy, and the final clinical effect is derived from a combination of these. However, these mechanisms have not been specifically looked at in preterm infants. Table 1 summarises the results of various physiological studies involving HHHFNC devices.

Table-1.

Purging of nasopharyngeal dead space

In between breaths, the nasopharyngeal dead space contains end-expiratory gas which dilutes the subsequent breath. By providing a flow equal to or above the peak inspiratory flow demand of the patient, HHHFNC can wash out this dead space and provide a reservoir of fresh gas so that a higher proportion of minute ventilation participates in gas exchange. In addition, as the administered gas flow is not diluted by room air, the FiO_2 delivered to the patient approaches close to the desired value. In a neonatal animal model study, HHHFNC increased CO_2 clearance with increasing flows up to 8 L/min without changing tracheal pressures, and the authors proposed increased flushing of anatomical dead space as the explanation for their findings. This effect is akin to tracheal gas insufflation during mechanical ventilation, which has been shown to reduce ventilation pressure and volume requirements in ventilated animal models and preterm infants.

Reduction in upper airway resistance

Another proposed mechanism of action for HHHFNC is reduction of upper airway resistance, which constitutes 50% of total airway resistance and can contribute substantially to work of breathing. This resistance is variable, owing to the expandable nature of the nasopharyngeal mucosa. It has previously been demonstrated that nCPAP reduces supra-glottic resistance by mechanical splinting of the airway with positive pressure. Saslow et. al. showed that neonates supported with HHHFNC (3–5 L/min) have a similar work of breathing compared to nCPAP (6 cmH2O). It is possible that HHHFNC may also have a similar effect, although there is no definitive data available to support this theory.

Provision of positive distending pressure

Many observational studies demonstrated that HHHFNC produces a positive distending pressure similar to nCPAP. Positive distending pressure can help recruit lung, prevent atelectasis, and decrease ventilation–perfusion mismatch in the lungs. Early studies on distending pressures by HHHFNC had small sample sizes and produced inconsistent results, urging caution in their interpretation. These studies concluded that the pressure generated is affected by the flow rate, leakage via the mouth (i.e. mouth open vs. closed), patient weight and nasal cannula size. On average, nasopharyngeal pressure was shown to increase by 0.45 cmH_2O for every 1 L/min increase in flow rate.

The degree of leak at the nares-prong interface is felt to be an important factor. Nasal cannulae with higher outer diameter produced higher mean pressures compared to cannulae with lower outer diameter. In vitro studies showed that airway pressure increased progressively with increased flow, and with nasal prong to nares ratio. In an animal study (Frizzola 2011), when 13

neonatal piglets with induced lung injury were treated with HHHFNC at 2–8 L/min in both high and low-leak settings, the impact of increasing high flow on CO2 removal and oxygenation was independent of the tracheal pressures generated. Both ventilation and oxygenation improved in a flow-dependent manner independent of leak, and oxygenation was particularly improved in the presence of higher leak. Current evidence suggests that less occlusive prongs achieved maximal efficacy with only 60% of the flow needed for occlusive prongs, and halved the inadvertent distending pressure. Optimized prong fit can produce better outcomes with less pressure, and manufacturers of HHHFNC therapy systems advise using prongs that are no greater than half the diameter of the nares for maximal efficacy.

Unlike bubble nCPAP, the delivered pressure with HHHFNC is variable depending on the phase of respiration and cannot be continuously controlled for or regulated, warranting regular clinical monitoring while infants are on HHHFNC therapy.

Conditioning of gas

The importance of warming and humidifying gas to support respiration has long been established. Fully conditioned gas is presumed to improve tolerance and comfort of patients, optimise muco-ciliary clearance, improve secretion quality and prevent atelectasis, and maintain normal mucosal function. The metabolic demand of warming and humidifying gases by the nasal mucosa in newborn patients with reduced pulmonary function can be significant enough to affect growth, which is already recognised to be poor. A retrospective study (Holleman-Dorey 2007) showed an improvement in growth amongst patients treated with HHHFNC in comparison to those given nCPAP. Though the authors did not attribute this growth effect solely to HHHFNC, they speculated that reduced energy demands secondary to respiratory support provided by HHHFNC may have contributed to improved growth.

In summary, observational studies of airway physiology during HHHFNC treatment have been inconsistent in their findings, possibly reflecting the variation in flow rates used, individual devices, nasal cannula size and mouth position and the actual pressures generated have not been consistently measured or determined. Nevertheless, HHHFNC utilization is increasing due to ease of application, patient tolerance, and theoretical clinical efficacy. Dead-space washout from HHHFNC may play an important role in the mechanism of action apart from generation of some distending pressure, although this has not been extensively studied.

Clinical Studies of HHHFNC Device use in Neonates

The use of HHHFNC started in neonatal intensive care units (NICUs) as an alternative to nCPAP, and has been described in recent surveys from the United Kingdom, North America and Australia. Although clinical use has increased rapidly, large randomised trials with adequate power to document safety and efficacy, have only recently been published. A Cochrane review by Wilkinson et al (2016) exploring the role of HHHFNC in respiratory support of preterm infants involving 15 clinical studies (1725 premature infants) have concluded that HHHFNC has comparable rates of efficacy to other forms of non-invasive ventilation for preventing treatment failure, death and chronic lung disease (CLD). They noted most evidence of HHHNC is available for its use in post-extubation respiratory support. We present a summary of the evidence from the main trials so far.

Table 1: Summary of Physiological studies on HFNC

Study Reference	**Gestational age and weight**	**Study type and design**	**Outcomes**	**Results and comments**
Locke et.al. 1993	Preterm infants, mean Gestational Age (GA) 30 weeks, mean birth weight (BW) 1,377 g, n = 13	Observational study. Unheated and un-humidified HFNC (Salter Labs), (0.5-2lit/min) prongs Outer Diameter(OD) 0.2 and 0.3 cm	Oesophageal pressure monitoring Ventilatory patterns with respiratory inductance plethysmography	No pressure generation with smaller prongs at any flow rate. Larger prongs deliver increasing pressure with increasing flow and reduced. Breathing asynchrony. Generated mean pressures of 9.8 cm H_2O at 2 L/minute.
Sreenan et.al. 2001	Preterm infants, GA 24-33 weeks, mean study weight 1,260 g, n = 40	Observational study. Unheated, humidified HFNC (Salter Labs) vs. NCPAP (Infant Star) flow rates 1–2.5 L/ minute, 'infant' size	Treatment of Apnoea of Prematurity (AOP), Oesophageal pressure monitoring	No difference in efficacy of treatment for AOP. Flow rate required to generate nCPAP of 6 cm H_2O increases with increasing infant weight.

		prongs used		
Saslow et.al. 2006	Preterm infants, GA 25-35 weeks, mean BW 1,118 g; mean study weight 1,542 g, n = 18	Observational crossover study, HHHFNC (3-5 lit/min) (Vapotherm 2000i) vs. nCPAP (Infant Bird)	Lung mechanics in infants with AOP, Respiratory Distress Syndrome (RDS), or Bronchopulmonary Dysplasia (BPD) and Oesophageal pressure monitoring	No difference in lung mechanics at any given flow rate; Oesophageal pressure was significant only at 5 L/minute of HHHFNC
Spence et. al. 2007	Preterm infants. Median study GA 30 weeks, median study weight 1,589 g, n = 14	Observational study, HHHFNC (1-5lit/min) and nCPAP (2-6cm H2o)	Intra-pharyngeal pressure	Pharyngeal pressure increases with increasing flow
Kubicka et. al. 2008	Preterm infants. GA range 25–40 weeks, birth weight 605–3,657 g. Study infants were more mature and larger. n = 27	Observational study. HHHFNC (1-5 lit/min), prongs OD 0.2cm.	Oral pressure monitoring	No pressure generated with mouth open at any flow rate, but with the mouth closed pressure increases with flow in infants < 1,500 g

Wilkinson et.al. 2008	Preterm infants. Median GA 27.1 weeks, median birth weight 944g. n = 18	Observational study. HHHFNC (Fisher and Paykell RT329). Flows up to 8lit/min	Pharyngeal pressure	Pharyngeal pressure increases with increasing flow but decreases with increasing weight. Mouth position is irrelevant
Lampland et.al. 2009	Preterm infants. GA <32wks and >72hrs old, mean birth weight 1,324 g, n = 15	Observational study. HHHFNC (1-6lit/min) vs. NCPAP Prongs size OD 0.24 cm.	End expiratory Oesophageal pressure and Clinical parameters of heart rate, respiratory rate, oxygen saturation, RDS score	As flow rate decreases below 2L/min, respiratory rate increases. As flow rate increases oesophageal pressure increases. high inter- and intra-patient variation in pressure. Other physiological parameters did not differ.
Sivieri et.al. 2013	In vitro study, Simulation model	Observational study. Evaluation of effect of flow rate and the ratio of nasal prong to simulated nares diameters on proximal airway pressures using a HHHFNC device. Neonatal and infant sized nasal prongs (3.0 and 3.7 mm OD) Seven sizes of simulated nares (range: 3-7 mm	Cannula and airway pressures and Cannula and mouth leak flows were measured during simulated mouth open, partially closed and fully closed conditions	Airway pressure progressively increased with both increasing HHHFNC flow rate and nasal prong-to-nares ratio. At 6 L/min HHHFNC flow with mouth open, airway pressures remained <1.7 cm H2O for all ratios; and <10 cm H2O with mouth closed for ratios <0.9. For ratios >0.9 and 50% mouth leak, airway pressure rises to 18 cm H2O at 2 L/minute flow followed by an increase

		internal diameter) Nasal prong-to-nares ratio range (0.43 to 1.06). Flow rates 1-6lit/min		to 24 cm H2O with pressure relief valve limited.
Frizzola et.al. 2011	Neonatal piglets 2-6 kgs, N=13	Randomized cross over study. Impact of HHHFNC and nCPAP on ventilation and oxygenation in an acute lung injury Model. HHHFNC rate 2-8lit/min Treated with nCPAP (min leak), single prong HHHFNC (high leak), double prong HHHFNC (low leak)	Measurement of respiratory, hemodynamic and blood gas parameters at each setting following 10 min of physiologic equilibrium	HHHFNC tracheal pressures were comparable to nCPAP pressures at the same flow range. With HHHFNC, improved ventilation in a flow-dependent manner independent of leak. double prong had greater impact on oxygen; single prong had greater impact on carbon dioxide (CO2) elimination. Better CO2 reduction achieved by high leak HHHFNC at lower flow rates.

Majority of the current evidence of HHHFNC therapy in neonates has come from studies involving preterm infants, though occasional studies extended their study to involve term infants. HHHFNC therapy is used in newborn infants as an alternative form of non-invasive respiratory support after extubation or as a primary therapy, and sometimes as a step down from other forms of non-invasive support. Table 2 summarizes the results of various clinical studies involving HHHNC.

Table 2: Clinical Studies of HHHFNC

Study Reference	Gestational age and weight	Study type and design	Outcomes	Results and Comments
Nair et. al. 2005 cited by Wilkinson et. al. 2016	Preterm infants HHHFNC group: mean Gestational Age (GA) 32 weeks, birth weight 1,675 g nCPAP group: mean GA 31 weeks, birth weight 1,493 g; N = 67	Prospective randomized study HHHFNC (5-6L/min) vs. nCPAP (5–6 cmH2O) prong sizes unknown	Need for intubation, Chronic Lung Disease (CLD)	No differences between two arms Trial ceased early due to withdrawal of HHHFNC units due to infection concerns. Abstract publication
Campbell et. al. 2006	Preterm infants HHHFNC arm: mean GA 27.4 weeks, birth weight 1,008 g; nCPAP arm: mean GA 27.6 weeks, birth weight 925 g, N = 40	Randomized Controlled Study (RCT) Unheated, humidified HFNC (1.4-1.7 L/min) vs. nCPAP (Infant Flow)	Prevention of extubation failure	Significantly higher rate of re-intubation with HFNC (12/20 vs. 3/20). Those who remained on HFNC had higher oxygen requirement than those on nCPAP.
Iranpour et. al. 2011	Preterm infants HHHFNC arm: mean GA 32.3 weeks, birth weight 1.82 kg; nCPAP arm: mean GA 32.5weeks,	RCT, nCPAP (6 cm H2O) vs. HHHFNC (1-4 L/min) after early extubation to nCPAP	Death, Necrotizing Enterocolitis (NEC), Patent Ductus Arteriosus (PDA), Intra Ventricular Haemorrhage (IVH), Brochopulmonary Dysplasia (BPD),	No differences noted in outcomes. HHHFNC group performed better in nasal mucosa score. Abstract in English. Full text in Arabic.

	birth weight 2.21 kg, N = 70		duration of O2, time in hospital and nasal trauma	
Yoder et. al. 2013	Preterm infants GA 28 to 42 weeks N = 432	Randomised controlled, un-blinded, non-crossover trial, nCPAP (maximum pressure 8 cm H2O) vs. current HHHFNC devices (flow of 3-5 L/minute) Either initial or post-extubation support	The primary outcome was need for intubation within 72 hours of starting non-invasive support	No difference between HHHFNC and nCPAP groups in early failure, subsequent need for intubation, in several adverse outcomes or several secondary outcomes. The HHHFNC group stayed on non-invasive support for longer.
Abdel-Hady et.al. 2011	Preterm infants HHHFNC arm: mean GA 31.1 weeks, birth weight 1,600 g; nCPAP arm: mean GA 31.0 weeks, birth weight 1,600 g; N=60	Randomised controlled trial. Weaning from nCPAP (Fisher and Paykell) with/without weaning to HHHFNC (0.5–2 L/ min) Ultramed prongs: 0.3 cm	Duration of respiratory support, days on oxygen and length of stay	nCPAP-only group had fewer days on oxygen (median 5 vs. 14 days) and shorter duration of respiratory support (10.5 vs. 18 days). Underpowered.
Collins et.al. 2013	GA<32 weeks No: 132 ventilated babies	Randomised controlled trial, HHHFNC (8 L/min) vs nCPAP (8 cm	Primary: Extubation failure up to 7 days. Secondary: Nasal trauma, duration of respiratory support & supplemental O2,	HHHFNC and nCPAP produced similar rates of extubation failure or BPD.HHHFNC was associated with

		H2O)	BPD (36 weeks), IVH, NEC, time to full feeds	significantly less nasal trauma compared to nCPAP.
Kugelman et.al. 2015	RC pilot study Preterm infants < 35 weeks GA and > 1000 g BW, 76 infants	HHHFNC (1-5 L/min) vs SNIPPV (Syncronized Nasal Intermittent Positive Pressure Ventilation) for primary treatment of RDS. Maximal flow on HHHFNC was 3.4 (±1.4) L/min	Failure of nasal therapy, need for intubation, Other comorbidities, Nasal trauma	No significant difference in the need for endotracheal ventilation and rate of co-morbidities were comparable between two groups. Underpowered.
Manley et.al. 2013	RCT, Multi-centre, non-inferiority study Preterm infants < 32 weeks GA, N= 303 infants	HHHFNC (5- 6 L/min) vs bubble CPAP (5-8 cm H2O)	Treatment failure within 7 days after extubation. Reintubation during the primary outcome period, death before hospital discharge, BPD and other co morbidities	HHHFNC was non-inferior to the use of nCPAP. Less nasal trauma in HHHFNC group and no significant differences in rates of serious adverse events or other complications
Badiee et.al. 2015	RCT, Preterm infants (28-36 weeks) stable on CPAP 5 cm H_2O, FiO_2	Switch to HHHFNC 2L/min and wean vs continuing on nCPAP 5cm H2O and wean to	Primary: Duration of O2 requirement. Secondary: Duration of respiratory support, rate of successful weaning and length of	Weaning from nCPAP to HHHFNC could reduce the duration of oxygen therapy and length of

	<30%, N= 88	room air	hospital stay	hospitalization in preterm infants. Infants in HHHFNC group were younger compared to CPAP group at start of weaning
Ciuffini et.al. 2014	RCT, N-177 (Planned sample size 316) Preterm 29-36 weeks with mild-moderate RDS	HHHFNC (4-6 L/min) vs nCPAP (4-6 cm H2O)	Primary: Need for intubation and ventilation, duration of respiratory support. Secondary: BPD, Pneumothorax and others	No difference in the primary outcomes Preliminary results only
Mostafa-Gharehbaghi et.al. 2014	RCT, N-123, 30-35weeks 1250-2000 grams, received surfactant	HHHFNC (6 L/min) vs nCPAP (5-6 cm H2O)	Primary: Intubation and ventilation within 3days after surfactant, BPD. Secondary: Pneumothorax, nasal mucosal injury, IVH	HHHFNC as effective as nCPAP as respiratory support. HHHFNC group has less nasal mucosal injury.
Liu et.al. 2014	RCT, N=255, Intubated newborns admitted to Neonatal unit< 7days of life	HHHFNC (3-8 L/min) vs nCPAP (6-10 cm H2O)	Primary: extubation failure, BPD and mortality. Secondary: duration of ventilation, nasal septum injury, others	HHHFNC appears to have efficacy and safety similar to those of nCPAP. Comparable secondary outcomes

Prevention of extubation failure

Most neonatal studies have focused on HHHFNC as respiratory support during the post-extubation period in premature infants. A pilot study (Campbell 2006) comparing HHHFNC to nCPAP as post-extubation support in 40 preterm infants resulted in significantly more infants in the HHHFNC group being re-intubated within 7 days compared to the nCPAP group. However, the HHHFNC system used was a non-heated bubble humidifier, and the flow rates used were typically lower than those in current clinical use. Collins (2013) studied failure (defined objectively) rates in the first 7 days after extubation in 132 ventilated premature infants (<32weeks gestational age [GA] at birth) when randomized to receive either nCPAP or HHHFNC. Comparable failure rates were observed between HHHNC group and nCPAP groups (22% vs 34%) with no difference in the number of infants re-intubated in the first week. A non-inferiority study by Manley (2013) on 303 very preterm Infants (<32 weeks GA at birth), comparing treatment with either HHHNC (5-6 L/min) or nCPAP (7 cm H_2O) after extubation, noted similar extubation failure rates between HHHFNC and nCPAP groups (34.2 vs 25.8%) with no significant differences in adverse events. ln a randomised trial of 432 infants, Yoder (2013) compared nCPAP with current HHHFNC devices as either primary or post-extubation support. Stratified data analysing post-extubation outcomes found no difference in early failure rates (<72 hours) between HHHFNC and nCPAP groups, in subsequent need for intubation or in several secondary outcomes, including air leak and incidence of bronchopulmonary dysplasia (BPD). They concluded that in neonates ≥28 weeks' GA, HHHFNC appears to have similar efficacy and safety to nasal nCPAP when applied immediately post-extubation. Only a third of the infants enrolled in this study were below 32 weeks of gestation, limiting the generalisability of the results to smaller infants. A study by Liu (2014) comparing HHHFNC to nCPAP as post-extubation respiratory support in 155 infants (<7days old) with a mean GA of 35.5 weeks showed comparable efficacy between HHHFNC and nCPAP in preventing extubation failure, death and mortality. Another randomized trial by Mostafa-Gharehbaghi (2014) on 123 preterm infants with mean GA of 32 weeks, testing the effect of HHHFNC against nCPAP following initial stabilization with nCPAP and surfactant therapy, showed equal efficacy between both groups in terms of preventing extubation failure. The latest Cochrane review (Wilkinson 2016) found no difference between HHHFNC and nCPAP in preventing extubation failure with no difference in the rate of treatment failure (relative risk [RR] 1.21, 95% confidence interval [CI] 0.95-1.55) and re-intubation rates (RR 0.91, 95% CI 0.68-1.20). However, the duration of mechanical ventilation, supplemental oxygen, time to full feeds and incidence of nasal trauma, all significantly favoured the HHHFNC group.

These data suggest that HHHFNC may be a useful respiratory modality to help reduce the need for intubation in premature infants with early respiratory distress, and could be a potential alternative to nCPAP in post extubation states. However, there is insufficient data available on the efficacy

and safety of HHHFNC in extreme preterm infants (< 28 weeks), and caution must be exercised when HHHFNC is used in this population.

Primary therapy for respiratory failure

Data from a study by Nair (2005) compared HHHFNC with nCPAP in a randomised study of preterm infants (mean GA 31 weeks) with respiratory distress syndrome (RDS), when randomised at 6 hours of age to continue on bubble nCPAP or change to HHHFNC (5 -6 L/min), showed similar outcomes in terms of respiratory failure between each group. In a study by Iranpour (2011) presented in abstract form, 70 preterm infants (GA 30-35 weeks) were randomised after early surfactant treatment and extubation to nCPAP or HHHFNC. They concluded that HHHFNC (after receiving nCPAP for the first 24 hours of birth) is as effective as nCPAP in the management of respiratory distress syndrome. Another pilot study from Israel by Kugelman (2013) compared early HHHFNC with NIPPV for the primary treatment of RDS in 49 neonates (GA < 35 weeks, birth weight [BW] ≥ 1000 g), and concluded that HHHFNC seems to be as effective as NIPPV in preventing endotracheal ventilation in premature infants with RDS. The primary respiratory support arm of the study by Yoder (2013) found longer duration of respiratory support in HHHFNC group compared to nCPAP group. The interim results of an Italian study (Ciuffini 2014) that enrolled 177 of a planned 316 preterm infants (GA 29-36 weeks) with mild to moderate RDS, when randomized to nCPAP or HHHFNC, showed no difference in need for intubation and ventilation, duration of respiratory support, incidence of BPD or pneumothorax between the two intervention arms. Wilkinson's (2016) Cochrane review found similar failure rates (RR 0.77, 95% CI 0.43-1.36) between HHHFNC and nCPAP when used as primary respiratory support including no significant differences in the incidence of death, BPD, nasal trauma and pneumothorax. However, data on efficacy and safety of HHHFNC as a primary respiratory support in extremely premature infants (< 28 weeks GA) and late preterm infants is limited, and should be subjects of future research. Evolving evidence suggests that the use of HHHFNC as a primary therapy appears to be safe and efficacious in > 28 weeks' premature infant population, and has a potential to become alternative to nCPAP.

Mode of weaning from nCPAP

The practice of weaning or 'stepping down' from nCPAP to HHHFNC treatment is increasingly becoming common. Presumably, this practice stems from the belief that HHHFNC is a mild form of nCPAP, and also that convalescing preterm infants with evolving BPD will benefit from the smaller nasal prongs and less bulky device. A randomised controlled trial (RCT) by Abdel-Hady (2011) on 60 preterm infants stable on nCPAP for at least 24hrs, who were either changed to HHHFNC (0.5-2 L/min) or continued on the same support, resulted in the HHHFNC group having

clinically significant increase in days on oxygen (median 14 vs. 5 days; $p < 0.001$) and duration of respiratory support (18 vs. 10.5 days; $p = 0.03$) which was attributed to use of low flow rates in HHHHNC group. However, no differences were found between groups regarding success of weaning from non-invasive support. A recent RCT (Tang 2015) on sixty infants born <30 weeks' GA, testing the weaning strategies for preterm infants on NIV, found use of HHHFNC may be effective at weaning infants from nCPAP, but did not reduce the duration of respiratory support or time to full suck feeds. A similar study (Badiee 2015) on 88 preterm infants concluded that infants weaning from nCPAP to HHHFNC could decrease the duration of oxygen therapy and length of hospitalization. Though the evidence for HHHFNC as mode of weaning from nCPAP is encouraging, there is a pressing need for further adequately powered studies to explore this intervention.

Safety Issues

Safety issues broadly include infection control, inadvertent excessive airway pressures, and consequent air-leak related problems, and nasal trauma. HHHFNC systems currently on the market have stringent infection control systems in place. This was given particular importance following issues around Ralstonia species found to contaminate the Vapotherm system in 2005. There have been reports of infants developing subcutaneous scalp emphysema with pneumo-orbitis and pneumo-cephalus after being supported with HHHFNC of 4 L/min. It is likely that the very low birth weight, premature infant population is at most risk of air leak with HHHFNC. The lack of pressure monitoring available in HHHFNC systems and inconsistency of pressure generated may further compound this issues warranting vigilance while infants are on HHHFNC therapy. Other possible risks include gastric or intestinal distension or perforation. The recent Cochrane review (Wilkinson,2016) showed no difference between nCPAP or HHHFNC in the incidence of several adverse outcomes, including intra-ventricular haemorrhage, chronic lung disease, sepsis, retinopathy of prematurity, or the rate of pneumothorax.

Advantages

Unlike older generation devices, modern HHHFNC devices seem to preserve the nasal mucosa well. As compared to nCPAP, nasal cannulae are less tight fitting with HHHFNC thus reducing the risks of trauma and are associated with either improved nasal injury scores (Woodhead, Iranpour) or comparable to those on nCPAP (Campbell). A recent meta-analysis (Kotecha, 2015) showed a significantly lower odds of nasal trauma (defined and measured variably) in preterm infants supported on HHHFNC, compared with other modes of nCPAP. Furthermore, in a recent survey (Roberts 2014), majority of nurses believed that HHHFNC were more comfortable for infants, caused less nasal trauma and were preferred by parents compared to nCPAP.

Clinical Guidelines and Weaning

Earlier studies on HHHFNC used flows (<2 L/min) which are believed to be too low to be clinically effective. However, current HHHFNC devices recommend initial flows above 3L/min and up to 8 L/min in neonates and infants. Recommended flow rates may vary depending on the weight and gestational age of the infant. There is limited data available on the methods of weaning HHHFNC, and the criteria for a failed attempt at HHHFNC withdrawal are unclear. A recent systematic review (Farley 2015) found no randomized trials exploring ideal technique of weaning HHHFNC. Some units wean the rate first while others wean the oxygen and no universally agreed guidelines exist. It is difficult to establish guidelines for weaning from HHHFNC therapy and its replacement by conventional oxygen therapy. However, it would seem reasonable to first lower FiO2 and then the flow, and a reasonable recommendation could be maintenance of the administered flow until correct oxygenation is achieved with FiO2< 0.3. The reduction in flow should be slow (0.5 L/min every 36-48 h) and once correct oxygenation has been achieved with ≤1-2 L/min and FiO2< 0.3, one could consider switching from HHHFNC to conventional low-flow oxygen therapy.

Summary

There has been rapid acceptance of HHHFNC therapy to neonatal and paediatric practice over the last decade largely due to apparent clinical efficacy and ease of use. Despite the rapid clinical acceptance, relatively little is understood about the precise mechanisms of action, and there is a lack of guidelines to assist clinicians regarding the use of HHHFNC. Current data from observational studies indicate efficacy can be greatly affected by factors such as choice of cannula size, mouth position or flow rate and therefore careful training of personnel in correct application technique is vital to success. Inability to measure the positive pressures generated has led to genuine concerns amongst some clinicians and it is crucially important that an excess of pressure is not administered, something that is of particular concern in the extremely premature population in whom safety and efficacy of HHHFNC is not well established. It is important that infants are reassessed clinically after commencing on HHHFNC in order to judiciously intervene in those who do not respond and may require escalation of respiratory support especially in settings where HHHFNC used outside of an intensive care setting.

Though earlier studies evaluating HHHFNC devices using relatively low flow rates showed mixed results, there is a growing body of literature documenting safety and efficacy of modern HHHFNC devises comparable to that of nCPAP in neonatal as well as paediatric population. There is a paucity of data on longer-term out-comes such as chronic respiratory morbidity and neurodevelopment status, and a lack of guidelines on weaning HHHFNC, which could potentially

become subjects for future research. It is probable that current ongoing and future trials might address these issues which would expand further the role of HHHFNC as a respiratory support in neonatal and paediatric practice over coming years.

Further Reading

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Practice Points

- HHHFNC is rapidly emerging as a popular method of non-invasive respiratory support in neonates that is generally well tolerated by patients and popular among medical fraternity due to ease of use
- The exact physiological mechanisms of action of HHHFNC are yet to be fully understood and the generated distending pressures are variable and unregulated.
- There is a growing body of clinical evidence supporting HHHFNC equivalence to nasal nCPAP. The results of future studies are likely to strengthen this evidence base and provide crucial data on safety and long term outcomes
- Careful and regular monitoring of response to HHHFNC treatment is important, especially if it is undertaken outside of an intensive care environment

A CASE OF PERICARDIAL EFFUSION IN A NEWBORN – CASE REPORT

Dr. Bhoojatha [1], Dr. S. Laxman , Dr.Vikram K [3]

[1]***Consultant Neonatologist***

[2] ***Neonatal Fellow***

[3]***Paediatric Cardiologist***

INTRODUCTION:

Pericardial effusion is abnormal collection of fluid in the pericardial cavity. Pericardial effusion as a part of hydrops fetalis is common in newborn. Idiopathic pericardial effusion in newborn is very rare. Previous case reports of isolated pericardial effusion in newborn are present only secondary to central venous catheter insertion. The estimated prevalence of pericardial effusion following CVC insertion was 1%.We report a case of isolated idiopathic pericardial effusion presenting on day 1 of life.

CASE DETAILS:

A male baby was born to primi mother at 38 weeks of gestation age with normal course throughout the pregnancy except for a history of fever 3 days prior to delivery. Caesarean section was done. APGAR were 7 at one minute and 9 at 5 minutes. Baby has tachypnoea following delivery with mild sub costal retractions. Baby was referred to our hospital for further management.

In our hospital, initial physical examination was made, while the baby was started on oxygen supplementation with nasal prongs. On examination – baby has tachypnoea with mild subcostal retractions with no cyanosis. On auscultation heart sounds were normal with no audible murmur. All the pulses were felt. Baby has no dysmorphic features/obvious external congenital anomalies. Chest X – ray showed cardiomegaly with normal lung fields. Initial blood screenings showed positive CRP. Other blood counts done were normal. Baby was started on oxygen support, Iv fluids & Iv antibiotics. Echocardiogram done revealed pericardial effusion with right ventricular mass. Hence baby was immediately taken for pericardiocentesis. Percutaneous pericardiocentesis was done on day 2 of life with insertion of indwelling pericardial catheter. 50 ml of the serous fluid has been drained. Evaluation for the cause of pericardial effusion has been done. Pericardial fluid has been sent for analysis, culture & sensitivity & viral PCR for parvovirus. Fluid analysis revealed transudate type of fluid with cell count of 40 cells with 100% lymphocytes

with no growth on culture & sensitivity. Viral screening sent was negative. Thyroid profile & TORCH screening sent for the baby were normal.

Pericardial drain has been removed on day 3 of life & baby has been serially monitored by 2D echo daily for re-accumulation of pericardial fluid. Repeat echocardiogram did not reveal any collection & baby has improved clinically. Iv antibiotics has been stopped as the final blood culture reports were negative. Biopsy of right ventricular mass has been deferred as baby condition improved. Baby has been discharged & is on follow up for monitoring the size of intraventricular mass. Upon follow-up, the size of the mass has been decreased.

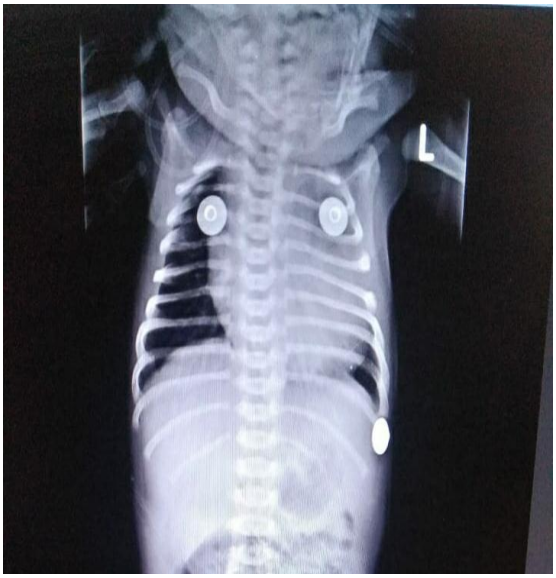


Fig 1: Chest X-ray demonstrating Cardiomegaly

DISCUSSION:

Common causes of pericardial effusion in a newborn are many varying from infections to congenital anomalies.

- **Hydrops fetalis**
- **Infections**
    - Parvovirus
    - HIV
    - Mycoplasma hominis
    - Coxsackie virus A & B
- **Structural abnormalities**
    - Intrapericardial teratoma & hemangioma
    - Congenital diaphragmatic hernia/ eventeration
    - Cardiac structural defects
    - Anterior abdominal wall defects

- **Chromosomal anomalies**

- **Transient fetal plenral & pericardial effusion**.
- **Congenital hypothyroidism**
- **Complication of Central venous catheter**

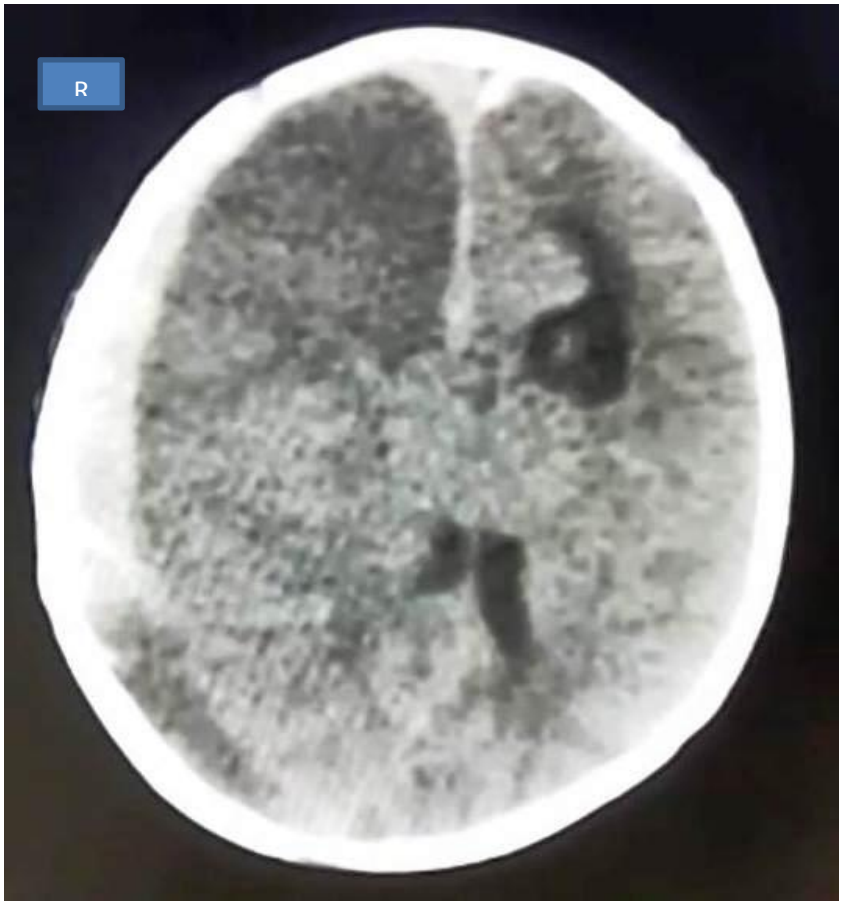
Most of the reported cases of isolated pericardial effusion in newborn are secondary to central venous catheter insertion. Clinical presentation may vary from being asymptomatic to clinically significant respiratory distress, muffled heart sounds & thread pulse. Massive pericardial effusion in a neonate is potentially fatal complication which needs timely recognition & prompt intervention. Treatment is by percutaneous pericardiocentesis with the supportive measures.

IMAGE QUIZ

Dr Syed Mudassir

Consultant Pediatrician, Andhra Hospital.

A 5-weeks-old male infant was brought to our emergency department with complaints of poor feeding , dull activity along with two episodes of convulsions(GTCS , lasting for 5 mins) and vomitings for 1 day. There was no h/o fever, trauma , birth asphyxia and no previous NICU admissions. Antenatal, natal and postnatal history was unremarkable. Upon examination, he was afebrile and dull along with bulging and non-pulsating anterior fontanelle. Remaining systems examination was normal. Subsequently, blood tests were ordered which revealed high PT,APTT levels and low haemoglobin levels . CT brain showed right subdural haemorrhage with midline shift.



CT Brain : Demonstrating Right sub-dural hematoma with midline shift.

Q1. What is the underlying diagnosis ?

Q2. How will you manage the child?

Q3. What precautions need to be taken to prevent such incidents?

Answers:

Q1. Late HDN

Q2. Inj vitamin k 0.3mg/per/dose iv. Consider FFP and surgery if significant bleeding.

Q3. To give inj vitamin k 1mg IM to all newborn infants.

DISCUSSION;

This infant was treated with inj vitamin K and FFP transfusion. Burr hole surgery was done by neurosurgeon due to massive bleeding and midline shift noted on the CT brain. After 2 days, child's condition has improved and discharged on oral levetiracetam.

Vitamin K deficiency haemorrhagic disease of newborn (HDN) is a well known entity and presents in 3 different clinical forms – early, classical and late. The coagulopathy is due to deficiency of vitamin K dependent procoagulant factors II, VII, IX, X. In the event of vitamin K deficiency Protein Induced in Vitamin K Absence (PIVKA) arc in excess and its estimation is very helpful in diagnosis even after starting the treatment. The bleeding defects are usually corrected within few hours after administration of vitamin K. All newborn babies require vitamin K prophylaxis. Oral route is effective like parenteral route but require higher and more doses. Intra muscular route is safe and does not increase the risk of childhood cancer. All breast fed babies with diarrhoea, malabsorption require another dose of vitamin K in postneonatal period to prevent late vitamin K deficiency bleeding

In the event of vitamin K deficiency, the non carboxylated forms of these proteins, PIVKA (protein induced in vitamin K absence) are detected in circulation. This can be estimated by HPLC (High pressure liquid chromatography), Enzyme Linked Immunosorbant Assay, or crossed immuno-electrophoresis. Presence of any amount of PIVKA is abnormal and is indicative of vitamin K deficiency. It remains in circulation for 48 to 72 hours after administration of vitamin K. So measurement of PIVKA even after treatment of acute bleeding episode will be helpful in making a diagnosis of vitamin K deficiency.In clinical practice 3 states of vitamin K deficiency are known. (a) Early haemorrhagic disease of new born (b) Classical haemorrhagic disease of new born (c) Late haemorrhagic disease (or) Late vitamin K deficiency bleeding (VKDB).

Early haemorrhagic disease of new born (Early HDN)

In early HDN bleeding occurs either in utero, during delivery, or during first 24 hours of life. The causes of bleeding are idiopathic and maternal intake of drugs that effect the metabolism of

vitamin K like warfarin, phenobarbitone, phenytoin, rifampicin, INH, salicylates and broad spectrum antibiotics. The extent of bleeding varies from skin bruising, subcutaneous haemorrhage, ecchymoses, umbilical bleeding to wide spread fatal intracranial, intra thoracic, intra abdominal bleeding but site of bleeding is usually concealed inside body cavities.

Classical Haemorrhagic Disease of New Born

Classical HDN typically occurs at 2nd to 5th day and its incidence is reported to be 0.25 to 0.5 per cent . It is due to physiological deficiency of vitamin K and its dependent procoagulants. These procoagulant levels in new born baby are 30-60 per cent of adult value and gradually increase to adult value by 6 weeks of age. New born babies are also deficient of vitamin K because of poor placental transfer, poor hepatic storage (one fifth of adult), delay in colonization of the gut by the flora known to synthesize vitamins, and mostly babies are breast fed and breast milk is relatively deficient in vitamin K. All these factors contribute in causing classical HDN. Affected infants are normal at birth but subsequently develop generalised ecchymoses, gastro-intestinal bleeding, nasal bleeding, bleeding after circumcision or bleeding from umbilical stump. The manifestations are not very severe and the disease can readily be managed with administration of vitamin K. Classical HDN is virtually non existent in infants given a parentral dose of vitamin K at birth.

Late Haemorrhagic Disease of New Born

Late onset vitamin K deficiency bleeding or late HDN is seen between 4-8 weeks in healthy breast fed infants. Vitamin K deficiency bleeding is an important cause of morbidity and mortality in infants older than 1 momth. This occurs in healthy breast fed infants and infants with underlying malabsorption like chronic diarrhoea, prolonged administration of antibiotics, hepatic cholestasis, biliary atresia, mucovicidosis and it may be idiopathic. Most of these infants present with acute intra cranial haemorrhage as the initial features and sometimes bleeding at puncture sites, ecchymoses and nodular purpuras.

Diagnosis

Age of onset of bleeding and relative healthy state of the infants usually gives a clue to the diagnosis. HDN infant does not look ill, toxic like septicemia and DIC. The clotting time (CT), prothrombin time (PT), partial thromboplastin time (PTT) and thrombo test are all prolonged while the thrombin time (TT) is normal.Other tests like estimation of PIVKA II level, coagulation factors II, VII, IX, × and estimation of native prothrombin antigen using monoclonal antibody is helpful in diagnosis of vitamin K deficiency bleeding.

Treatment

Vitamin K is available in 3 forms – Vitamin K1, K2 and K3. Vitamin K1 a phyloquinone derivative, is widely distributed in plants, natural in origin, fat soluble and in substantial doses reduces prothrombin time to normal in 6 to 12 hours time. Vitamin K2, napthoquinone derivative, naturally occuring, fat soluble and synthesized in alimentary tract by bacteria. K1 and K2 are rapid in action and nontoxic in high doses. Vitamin K3 is a synthetic sodium bisulfite and tetrasodium salt of menadione derivative, water soulable, takes 24 hours to act and has longer duration of action. In larger doses produces haemolytic anaemia, hyperbilirubinemia and kernicterus. Parenteral preparations are available (ampules containing 10 mg of vitamin K, Oral preparations as tablets containing 10 mg of acetomenopthane).

In infants 1-2 mg of vitamin K is adequate enough to correct even a severe vitamin K deficiency bleeding. The bleeding defect is usually corrected within few hours after parenteral administration of vitamin K. When the deficiency is severe it is advisable to administer vitamin K intravenous (IV) route because intramuscular (IM) route takes longer time for correction and may produce local haematoma.

For life threatening haemorrhages alongwith IV administration of vitamin K, 10-20 ml per kg body weight fresh frozen plasma should be administered. If the blood loss is more than 20 per cent and there is evidence of shock, immediate blood transfusion is essential for life saving.

Prevention

Haemorrhagic diseases of new born are preventable by administration of vitamin K. Infants predisposed to manifest early HDN as evidenced by maternal intake of drugs should receive vitamin K, 1 mg IV at birth and they may be delivered by cesarean section to avoid the trauma due to vaginal delivery. Even for its prevention high risk mothers may be administered vitamin K orally 7-10 days before delivery.

American Academy of Pediatrics (AAP) (Vitamin K task force U.S.A. 1993) has recommended :

(a) Vitamin K should be given to all new born babies in a single IM dose of 0.5 to 1 mg.

(b) Oral regimen should have 2 mg dose at birth which should be repeated at 2 and 4 weeks.

(c) A repeat dose should be given to breast fed infants with diarrhoea.

Current Controversies

Do all new born require prophylaxis?

As on today all clinical and biochemical evidence support the use of vitamin K prophylaxis to all babies and AAP recommends vitamin K prophylaxis to all new born babies.

Will an oral dose be sufficient? or IM Injection necessary?

Both the routes have their own merits and demerits. Studies have shown that oral vitamin K is sufficient to prevent classical HDN like IM route. But single oral dose in breast fed infants is not as efficient as a single parenteral dose in preventing late HDN. IM vitamin K have lower incidence of failure because of more reliable absorption but it has its hazards of injection whereas oral route has better acceptance, administration is better suited in developing countries, less complicated but there may be a chance that medicine may be vomited, absorption may vary and not easily available in India.

Is vitamin K required in post-neonatal period?

Late vitamin K deficiency bleeding in infants in post-neonatal period is well known established entity. To prevent this it is recommended for all breast fed babies with diarrhoea or malabsorption another dose of vitamin K in post neonatal period.

Does IM vitamin K injection cause cancer?

The publication of the article by Jean Golding from UK in 1992, linking IM administration of vitamin K with increased risk of childhood cancer has generated a great deal of discussion in this subject. But however Klebannof et al (U.S.A) in 1993 found no association between perinatal IM vitamin K administration and risk of childhood cancer. Other reports from Sweden, Denmark, and Britain are also not agreeing with the report of Golding. USA study involved more than 3 times as many children as British study and was better designed, it should be considered the final word that the vitamin K injection is safe. Considering the life threatening potential of vitamin K deficiency and the risk of cancer yet unproven, it is perhaps unjustifiable at this time to abandon IM prophylaxis atleast until more effective studies are available.