ORIGINAL RESEARCH

Effect of change in sequence of administration of pentavalent and pneumococcal vaccines on perception of pain in healthy infants : "Randomized Control Trial"

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ABSTRACT

Objective: To determine pain response of infants to change in sequence of Pentavalent and PCV vaccine injection.

Design: Single-center, randomized, parallel group, active controlled trial

Setting: Immunization clinic, Department of Pediatrics, LLRM medical college, Meerut, India.

Participants: Healthy full term infants upto 4 months of age.

Intervention: Infants received either pneumococcal conjugate vaccine(PCV) or Pentavalent vaccine first, followed one minute later by the other vaccine. Infants were videotaped from 5 to 10 seconds prior to first vaccine injection till 3 minutes after second vaccination using a handheld video camera. The primary outcome measure was infant pain assessed by modified facial coding system (MFCS) and neonatal infant pain scale (NIPS) from the videotapes by research assistants.

Results: 130 participants were enrolled in study after consent 65 in each group. Outcome data for 128 infants were available for primary outcome analysis because of missing data of 2 infants in group A. Pain scores, MFCS and NIPS per infants were significantly lesser in group B than group A upto 1 minute after second vaccination. Similarly lesser change in hemodynamic parameter like heart rate and SpO2 was observed in group B. Total cry duration was also observed lesser in group B.

Conclusion: Simple change in order of vaccine is an effective non-pharmacological intervention in reducing pain during vaccination of infants. Infants experience lesser pain when Pentavalent vaccine is given first followed by PCV, instead when PCV vaccine is given first.

Keywords: PCV (Pneumococcal conjugate vaccine), SpO2 (Oxygen saturation), MFCS and NIPS, Infant pain, Pentavalent vaccine.

INTRODUCTION

Vaccination is a proven and one of the most cost-effective child survival intervention preventing millions of lives every year[1]. With advances in medical sciences many vaccines are developed to combat vaccine preventable diseases (VPD). Although technologies have developed many combination vaccines, multiple vaccination in single visit and repetitive vaccination is a norm in all immunization programs his multiple and repetitive vaccination in infants is associated with significant pain in children which may even result in drop out and refusal for further vaccination by parents because of parental anxiety and distress(1). Moreover pain is source of concern and anxiety for new parents and may disturb mother-infant bonding(2). The pain associated with such injection is source of distress for children, their parents and health care provider too. If not addressed, this pain can lead to pychological trauma, procedural anxiety, needle fears and health

care avoidance behaviors, including non adhereance with vaccination schedule in future(3)Although it is not possible to completely eliminate pain during needle injections but methods have to be evolved to mitigate pain in infants. These measures to reduce the amount and intensity of pain is important as it is an ethical expectation by parents but also because repeated painful exposures can have deleterious consequences on children's cognitive development and their future responses to painful events (4–6). Recently many studies are conducted to decrease procedural pain in neonates admitted in neonatal intensive care unit and few are conducted to decrease infant pain response during vaccination. Being an outdoor procedure, these methods needto be fast, inexpensive and feasible in immunization clinic. Many pharmacological, physical, non-pharmacological, psychological methods have been tried. As different vaccines cause pain of different intensity a simple change in sequence of vaccine can improve pain perception response post vaccination. We therefore designed a study to determine if the degree of pain perception in infants after administration of the Pentavalent (DwPT, Hepatitis B, Hib) and Pneumococcal conjugate vaccine (PCV) is affected by the order in which they are given in a young infant upto 4 months of age. According to Indian academy of pediatrics guideline pentavalent (DwPT, Hepatitis B, Hib) and pneumococcal conjugate vaccine (PCV) are given at 6, 10 and 14 weeks.

2. METHODS: Our department had already done a similar study to determine effect of sequential change in hepatitis b and DwPT vaccine on infant pain response *(7)* so our methodology was based on the same study and explained in detail there.

2.1:Study design: Single center, double blind, randomized clinical trial in immunization clinic of pediatrics department in llrm medical college, Meerut

2.2 Ethical clearance and consent: This study was initiated with clearance from the ethics committee of our college. Each subject was enrolled with written informed consent of the parent or guardian after explaining the whole study in their local language. Patient records were kept confidential and anonymous.

2.3: Participants

2.3 (i): Inclusion criteria

Healthy full-term infants, upto four months of postnatal age, who attended immunization clinic for vaccination of PCV and Pentavalent vaccine as per the immunization program.

2.3(ii): Exclusion criteria: All infants who were admitted in hospital for more than 48 hours, perinatal asphyxia (1 min Apgar score <7) or delayed cry if born at home, Pre-term deliveries (< 37 week of gestation), Intra-uterine growth retardation (IUGR) i.e., weight < 10th centile for gestational age, Previous surgery, Any congenital anomaly, Any chronic medical conditions,

2.4: Randomization

2.4 (i): Sequence generation

Random sequence generation was independently handled by independent statician using online software separately without involvement of other team members. Infants were randomly allocated to 1 of 2 groups in a 1:1 ratio by block randomization with computer generated randomly permuted blocks of 8. The numbers were written on small slips and placed in sequentially numbered opaque sealed envelopes (SNOSE METHOD).

The subject was randomized into two groups

- Group A - PCV vaccination prior to Pentavalent vaccination
- Group B- Pentavalent vaccination prior to PCV vaccination

2.4 (ii): Allocation and concealment

The staff on duty, who was not involved in intervention opened the sealed envelope, loaded the two syringes with PCV and Pentavalent vaccine and labelled them according to order in which it is to be administered with opaque tape with 'first' and 'second' written on tape.

2.4 (iii): Intervention and blinding

All eligible participants who consented for the study with written, informed consent taken from caretaker in their local language (Hindi) after explaining the full procedure. Babies were brought to the room where vaccination was to be done. Infants were then placed comfortably on immunization table in supine position. Doctor on duty recorded the demographic profile, clinical characteristics and hemodynamic parameters of all enrolled infants. As per the interventions stated in the sealed envelope, infant was vaccinated either with PCV vaccine first (group A) or the Pentavalent vaccine first (group B), administered intramuscularly at anterolateral aspect of one thigh by 0.6 x 25 mm (23 gauge) needle. 0.5 ml each of PCV vaccine (Synflorix Pneumococcal vaccine, Glaxo Smithkline Pharmaceuticals limited) or Pentavalent (Sanofi Pasteur, Shantha in Hyderabad India) was given. Second vaccine was administered in opposite thigh after 1 minute. Universal process of injecting vaccine was followed, the needle was inserted intramuscularly at 90° to the skin surface with steady pressure. No aspiration was performed(8) and the vaccine material was rapidly injected over 1 to 2 seconds followed by rapid withdrawal of the needle. During this procedure, vaccine injector called "done" when he removed the needle. Infants were videotaped from 5 to 10 seconds prior to first vaccination till three minutes after second vaccination using a handheld video camera. This

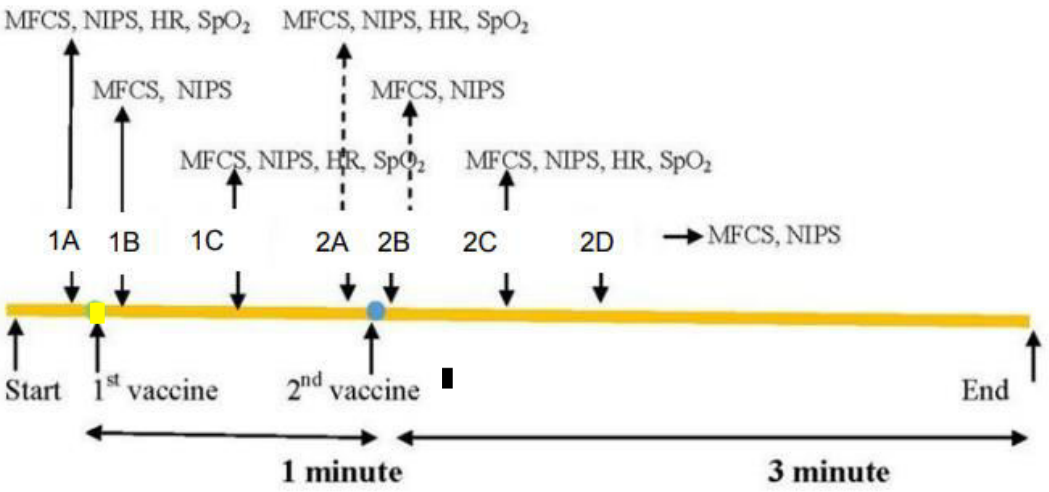
immunization procedure was standardized in all babies.The nursing staff assigned to open the sealed envelope and label the syringe was not involved in any other aspect of the study. So also the Doctor injecting vaccine and parents too were kept uninformed of the vaccine sequence. Third blinding was done at the level of search assistants, assessing the infant pain score by videotapes.

2.5: Assessed primary outcome:

2.5 (i) Infant pain score: we used same pain scale MFCS and NIPS as in our previous study.

Modified facial coding system (MFCS) –

It is a modified or shortened version of Neonatal Facial Coding Score (NFCS) given by Craig and Grunau(9). It includes five facial expression indicators, viz. brow bulge, eye squeeze, nasolabial fold, mouth open and chin quiver. Truncal movement was added as it supplements evaluation of facial movements in assessment pain. Each indicator was scored from 0 to 1 with 0 indicating absence and 1 indicating its presence. Total composite score was calculated by adding the score of each indicator which ranges from 0 to 6.The Neonatal Infant Pain Scale (NIPS)-This behavioral scale developed by Lawrence et al(10) is composed of six indicators facial expression, cry, breathing patterns, arms, legs, state of arousal. Each behavioral indicator is scoredwith 0 or 1 except "cry", which has three possible descriptors therefore, being scored with a 0, 1 or 2. Total NIPS pain score is sum of total of score of each indicator. Total score ranges from 0-7NPS = sum of all 6-indicator score, minimum score=0, maximum score=7NIPS and MFCS infant pain scores were assessed prior to 1st and 2nd vaccination, immediately and at 30 seconds after the 1st vaccination and 2nd vaccination. Also NIPS and MFCS score were assessed at 1 min after 2nd vaccination (Fig. 1).(7)



- 1A – Immediately before 1st vaccine injection: Parameter observed or analyzed - MFCS, NIPS, HR, and SpO_2.
- 1B- Immediately after 1st vaccine injection: Parameter observed or analysed - MFCS, NIPS.
- 1C - 30 seconds after 1st vaccine injection: Parameter observed or analysed - MFCS, NIPS, HR and SpO2
- 2A- Immediately before 2nd vaccine injection: Parameter observed or analysed - MFCS, NIPS, HR, and SpO_2.
- 2B- Immediately after 2nd vaccine injection: Parameter observed or analysed - MFCS, NIPS.
- 2C - 30 seconds after 2ndvaccine injection: Parameter observed or analysed - MFCS, NIPS, HR and SpO2
- 2D - 60 seconds after 2nd vaccine injection: Parameter observed or analysed - MFCS, NIPS.
- MFCS- modified facial coding system
- NIPS- neonatal infant pain scale
- HR- heart rate
- SpO2- saturation of oxygen

Figure 1: Timeline of the measure of outcome

2.6 Assessed secondary outcome

Infants' vital parameters like Heart rate (HR) and SpO_2 were recorded prior to vaccination, 20-30 seconds after the 1st vaccination and during the 2nd vaccination by pulse oximetry with **truesat pulse oximeter**. Infant size pulse oximeter probe was applied to right wrist of all participants.

Total cry duration is defined as total period of audible distress i.e., Start of first cry to cessation of all crying during four minutes period of entire study procedure.

2.7: Sample size

The sample size was calculated on the basis of a previous trial done in our center(7). Sample size of 64 in each group was calculated to detect clinically meaningful difference of 1 in pain score between group, for 2 tailed α value of 0.05 & power 80% and SD of 2. We recruited 65 infants in each group to account for some missing data as shown in flowchart (Fig. 2).2.8 : Statistical methodDemographic characteristics, clinical and hemodynamic parameters were compared between the two groups using paired t-test for continuous variable and chi-square test for

categorical variable. Wilcoxon rank sum test (Mann Whitney test) was used to analyze non- uniformly distributed data. Pain score (MFCS and NIPS), heart rate, SPO2 and total cry duration was plotted on box and whisker plot. The statistical significance level was $p < 0.05$. All analyses was done using Microsoft excel 10 and free e pi info software.

RESULTS

3.1 : Primary outcome- Demographic characteristics were comparable in both groups (Table 1)

Table 1 : Demographic Characteristics of the participants

Characteristics	Group A (n=65) Mean± SD	Group B (n=65) Mean± SD	Difference 95% CI	p value
Age (months)	2.35±0.77	2.45±0.75	2.27-2.53	0.457
Male/F	31/34	30/35		0.86
Weight (Kg)	5.25±0.78	5.21±0.83	5.096-5.374	0.79
Length (cm)	58.14±2.77	58.42±2.71	57.81-58.76	0.56
Head circumference (cm)	38.98±1.89	38.9±1.73	38.63-39.25	0.80
Time interval since last feed and start of vaccination (minutes)	42.61±12.12	41.77±12.82	40.03-44.35	0.699
Previous history of vaccination	65	65		1

Data expressed as Mean ±SD

Group A- First PCV Vaccination, Group B- First Pentavalent vaccination

3.1 (i): Pain scores

3.1 (I) (a): MFCS pain score

In our study, we found that median MFCS pain score was significantly lower immediately after first vaccination ($p < 0.001$), at 20-30 seconds after first vaccination ($p<0.001$) and prior to 2nd vaccination ($p<0.001$) in group B compared to group A (fig 3 and table 2).

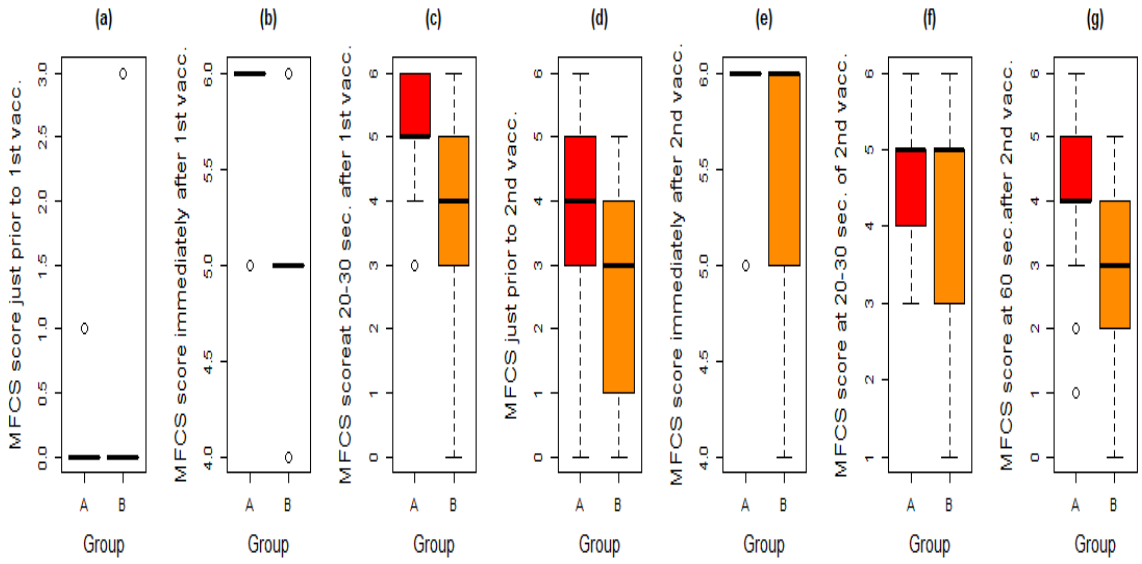


Figure No. 3: BOX AND WHISKER PLOT OF MFCS

3.1 (ii) : NIPS pain score

This study also found that median NIPS score were significantly lower after first vaccination, and 30 sec after first vaccination in group B than group A ($p<0.001$). Similarly, Median NIPS score was significantly lower prior to second vaccination and immediately after second vaccination in group B than group A ($p<0.05$) as depicted in figure 4 and table 3.

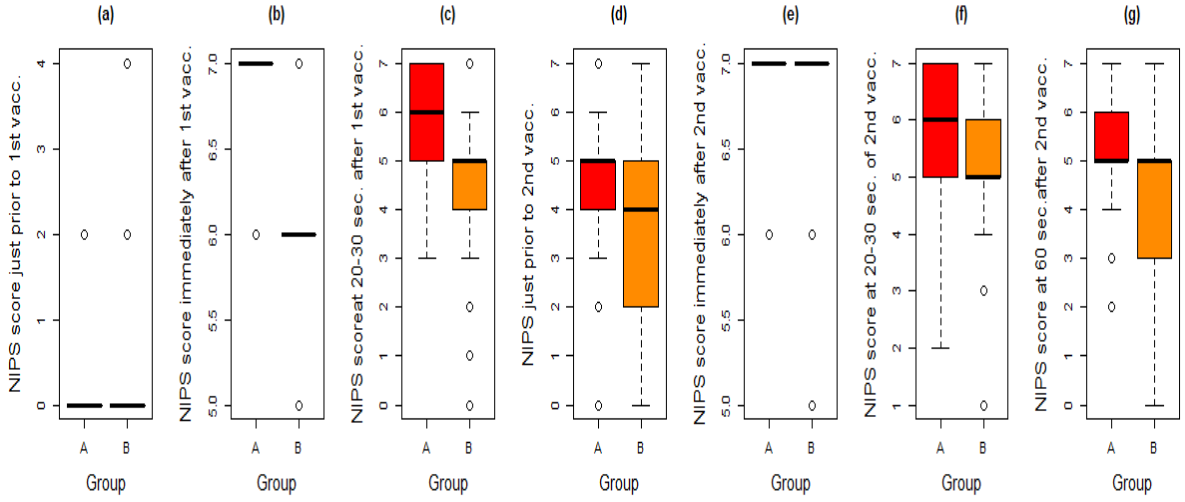


Table 2: MFCS Pain score

Parameters	Group A (n=63)	Group B (n=65)	p value
MFCS prior to procedure	0(0-0)	0(0-0)	0.99
MFCS immediately after 1st vaccination	(6-6)	(5-5)	<0.001
MFCS at 30 sec after 1st vaccination	(6-5)	(5-3)	<0.001
MFCS prior to 2nd vaccination	(5-3)	(4-1)	<0.001
MFCS immediately after 2nd vaccination	(6-6)	(6-5)	<0.05
MFCS at 30 sec after 2nd vaccination	(5-4)	(5-3)	<0.05
MFCS at 1 minute after 2nd vaccination	(5-4)	(5-3)	<0.001

Data expressed as Median (IQR)

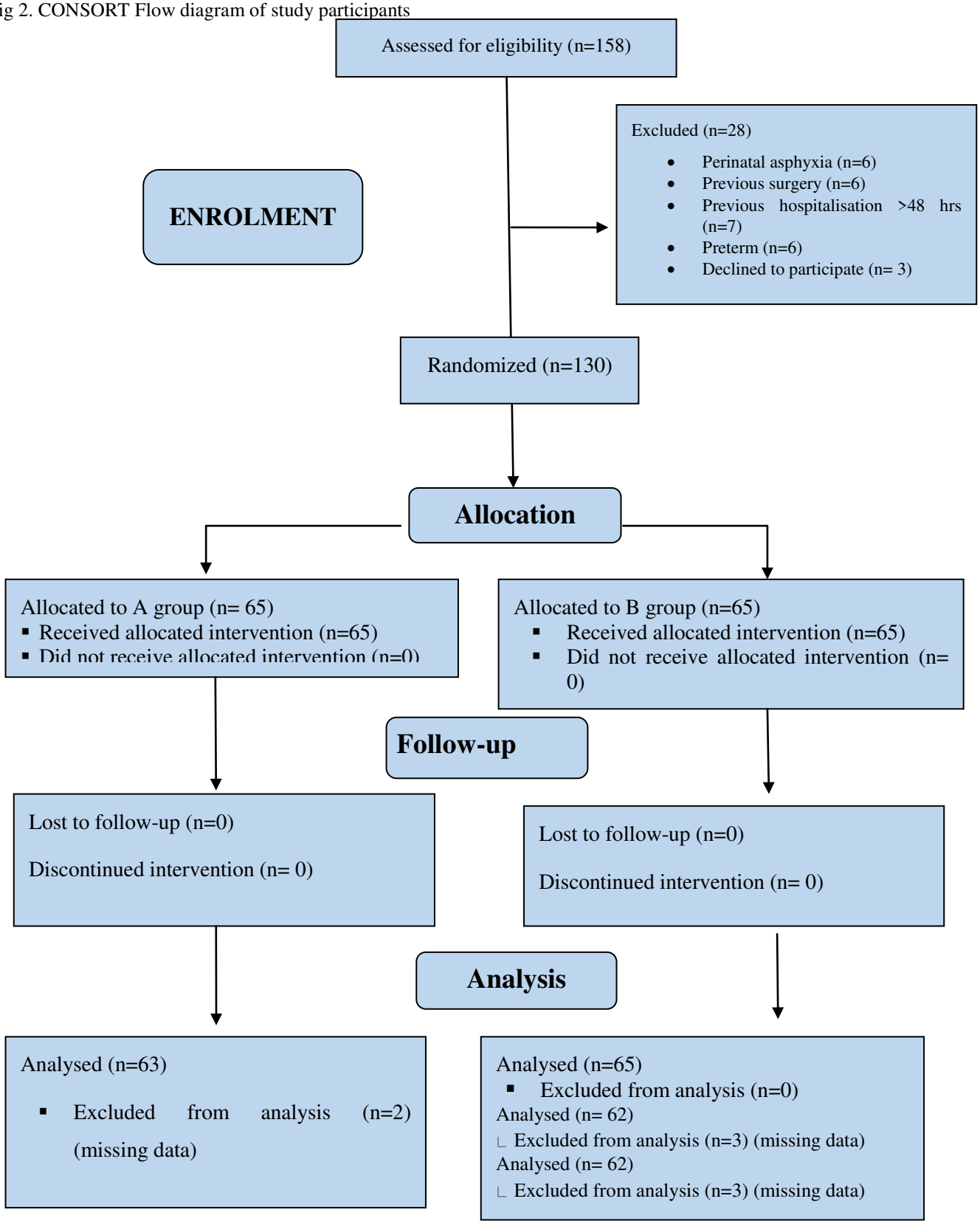
Group A- PCV Vaccine first, Group B- Pentavalent Vaccine first

Table 3: NIPS score

Characteristics	Group A (n=63)	Group B (n=65)	p value
NIPS prior to procedure	0(0-0)	0(0-0)	0.57
NIPS immediately after 1st vaccination	(7-7)	(6-6)	<0.001
NIPS at 30 sec after 1st vaccination	(7-5)	(5-4)	<0.001
NIPS prior to 2nd vaccination	(5-4)	(5-2)	<0.05
NIPS immediately after 2nd vaccination	(7-7)	(7-7)	<0.05
NIPS at 30 sec after 2nd vaccination	(7-5)	(6-5)	<0.05
NIPS at 1 minute after 2nd vaccination	(7-5)	(5-3)	<0.001

3.2 : Secondary outcome

Fig 2. CONSORT Flow diagram of study participants



3.2 (I,II) : Heart rate and oxygen saturation:
Out of 130 infants enrolled, data of 129 infants were available for analysis of heart rate. For one infant, heart rate could not be recorded during procedure due to malfunction of pulse oximeter Mean heart rate was significantly lower and mean SpO2 were significantly higher in group B than group A, at 20-30 seconds after first vaccination, prior to second vaccination and at 20-30 sec after second vaccination ($p < 0.001$)

3.2 (iii): Total cry duration
For total cry duration, out of 130 infants, data of 129 infants was available for analysis as video of one of the infants was of poor quality. Median total cry duration was significantly lower in group B as compared to group A ($p < 0.001$).

DISCUSSION

6.1: Summary of results

The study was conducted from June 2017 to June 2018In the present study, effect of change in the sequence of PCV and Pentavalent vaccine on pain was evaluated in healthy term infants up to 4 months of age. We observed that giving Pentavalent vaccination first followed by PCV vaccine injection in opposite limb resulted in lower pain scores and also shows lesser change in physiological parameters like heart rate and saturation of oxygen (SpO2). As well as, difference in total cry duration was observed in the two groups.

Validity of pain measure
We used two pain scales namely, Modified Facial Coding System (**MFCS**) and Neonatal Infant Pain Scale (**NIPS**) for reliable pain evaluation in our infants. Neonatal facial coding system provides sensitive, reliable, and valid measurements of short-term acute pain in both preterm and full-term babies up to 18 months (9–11). It has excellent inter-rater reliability, intraclass correlation > 0.85(7). Modified Facial Coding System which is a simplified modification of Neonatal Facial Coding System has been used previously by Upadhyay et al to demonstrate analgesic effect of expressed breast milk in infants during venipuncture(12). Similarly MFCS was used in other studies to measure infant pain response (13,14). Neonatal infant pain scale is also a validated pain scale used in various studies to observe pain perception of infants under12 months of age(7,15). We used multiple parameters for infant's pain assessment using pain scores, cry duration and physiological parameters like heart rate and oxygen saturation. Multidimensional assessment of pain have been shown to be more reliable than any single parameter as measure of pain be it pain score or cry duration and type(11)Even till date, administering most painful vaccine last is one of the less studied and reported method to decrease pain and distress in infants receiving multiple vaccination in single visit. Ipp et al, used MBPS score of infant and VAS score done by parents for assessment of perception of pain in infant post vaccination to compare change in sequence of DTaP-Hib and PCV. The pain scores were significantly lower in infant receiving quadrivalent DTaP-Hib vaccine first than in infant who received pneumococcal conjugate vaccine first (16) as in our study. Ravikiran et al, compared NIPS and staff nurse accessed VAS scores to determine effect of sequential change amongst BCG and Hep -b and concluded injecting BCG first will cause lesser pain than Hepatitis B first (15). Similarly Mithilesh et al, showed switch in order of vaccine to Hep B first followed by DwPT causes lesser pain by comparing NIPS and MFCS scales(7). Hanson et al , compared simultaneous versus sequential vaccine administration (3vaccines sequentially DPT-Hib, Hep B, prevenar vs. 2 simultaneous and 1 later) in single visit in 4 month healthy infants and accessed NIPS score concluding it was significantly lesser in group receiving simultaneous vaccine (17). Similarly Mc Gowan et al used MBPS and VAS scores to access infants distress to study impact of sequential change in DPT -hib-IPV and pneumococcal vaccine and reported although there was no significant difference in parents perception about distress experienced by infants in the 2 groups but there was significant difference in pain scale(18). Breast feeding, sucrose or any other sweet solution testing pre and during vaccination, and other physical and psychological interventions have been studied and found effective measures to reduce pain associated with vaccination (19). Total cry duration in our study was significantly lower in our study in group B compared to group A this was not seen in study by Mithilesh et al (7,12). There are no guidelines for time interval between two vaccine injections at one setting. We kept approximately one minute gap between two vaccine injections to allow the infant to settle, without unduly prolonging the whole procedure.

6.4: Limitation

We allowed the parents to touch and console their baby after injection in both the groups. Although it may impact the pain scores and total duration of cry, it was thought to be unethical to prevent parents from consoling their crying infants. Also, since this was common in both the groups, it is unlikely to affect the result. We did not study other neurophysiological parameters to measure cortical responses of infants brain to painful/nociceptive stimuli for pain assessment through the use of electroencephalography (EEG), functional MRI or Near infrared spectroscopy (NIRS) (20). Skin conductance indices are other physiological methods showing correlation with brain response to nociceptive stimuli which could have been studied (21). We tried to eliminate this bias by doing multiparameter analysis.

CONCLUSION

Simple change in sequence of vaccine is an effective, feasible, non-time consuming free of cost non-pharmacological procedural intervention which results in pain reduction during vaccination of infants. Infants experienced lesser pain when Pentavalent vaccine was given first followed by PCV instead, when PCV vaccine was given first. Pentavalent being less painful than PCV vaccine we can extrapolate the findings for normal healthy infants.

7. Recommendation: Administering Pentavalent vaccine first is an easy, effective, cost-free procedural intervention which can be combined with other physical/psychological or procedural intervention to reduce pain and distress experienced by infants receiving vaccine. Studies are needed to compare simultaneous versus sequential change of vaccine.

8. Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

9. Conflict of interest: Nil

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