"A PROSPECTIVE RANDOMISED CONTROLLED TRIAL COMPARING THE EFFICACY OF TOPICAL LOCAL ANAESTHETIC SPRAY WITH VAPOCOOLANT VERSUS EMLA CREAM FOR PAIN ALLEVIATION IN INFANTS DURING VACCINATION"

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LIST OF ABBREVIATIONS USED

DPT	Diphtheria-Pertussis-Tetanus
ECG	Electrocardiogram
EMLA	Eutectic Mixture of Local Anaesthetics
F	Friedman's Test
IAP	Indian Academy of Pediatrics
KW	Kruskal-Wallis
LA	Local Anaesthetic
MBPS	Modified Behavioural Pain Scale
MRC	Medical Research Centre
OPD	Outpatient Department
SD	Standard Deviation
VAS	Visual Analog Scale
WHO	World Health Organisation

ABSTRACT

Background and objectives

Pain during immunization is a major cause of concern as it is the most common iatrogenic source of distress. Positive impact of immunization on disease prevention and control is immense. Despite of having the best of medical facilities and advancements in the field of paediatrics we still consider immunization pain as something which is inevitable, which every infant has to go through. All children have a pain memory, and have the ability to anticipate painful procedures which may have effects on subsequent pain perception and response. All these factors lead to vaccine dropouts and increased non-compliance on the part of children themselves, parents and strikingly the provider too. There is a need for evidence-based study on usage of topical anaesthetic agents to alleviate the pain during vaccination in the subset of population of this region. The purpose of this study was to compare the prospective outcomes of using local anaesthetic spray and EMLA cream and encourage the usage of topical anaesthetics during immunization.

Materials and methods

An open label three-arm, randomized controlled trial which was done in KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi and Rukmini Nagar Urban Health Centre, Belagavi from September 2020 to September 2021. The objective was to compare the pain reduction efficacy of topical local anaesthetic spray with vapocoolant and EMLA cream during immunization. 228 children between the age of 9 and 11 weeks who were brought for immunization with 2nd dose of liquid pentavalent vaccine were enrolled and randomized into three groups and were

subjected to intervention accordingly. Modified Behavioural Pain Scale was used by the observer to assess the pain experienced by the infant before the injection, after 1 minute and after 5 minutes of injection. Parents also recorded their interpretation of pain experienced by their children using Visual Analog Scale. The data was analysed using statistical software R version 4.1.1 and Microsoft Excel. Shapiro-Wilk's test, Kruskal-Wallis test, Chi-square test and Friedman's tests were used.

Results

It was observed that the post-injection MBPS pain scores were significantly low in the two intervention groups when compared to control. The mean MBPS score at 1 minute was least in the group using topical LA spray with vapocoolant (5.11±1.1) followed by EMLA group (6.22±1.14) whereas control group (7.62±0.89) exhibited the maximum pain score values. The same trend was also observed when parental VAS scores were compared. The mean VAS score is least in group using topical LA spray with vapocoolant (3.66±1.66) followed by EMLA group (4.5±1.31) whereas control group (5.82±2.56) exhibited the maximum pain score values as per parents. We also observed that the parents were good at predicting pain in their children. There was no difference in pain scores with respect to gender observed.

Conclusion

The study proves that LA spray is beneficial in reducing injection pain during vaccination of infants and can potentially be used in immunization clinics conveniently, easily and cost effectively.

Keywords: Pain, Immunization, Vaccination, Topical, EMLA, Spray

CONTENTS

SR. NO.	TOPIC	PAGE NO.
1.	INTRODUCTION	1
2.	OBJECTIVES	4
3.	REVIEW OF LITERATURE	5
4.	METHODOLOGY	22
5.	RESULTS	27
6.	DISCUSSION	39
7.	CONCLUSION	46
8.	SUMMARY	47
9.	BIBLIOGRAPHY	49
10.	ANNEXURES	
	ANNEXURE I – Ethical Clearance Letter	58
	ANNEXURE II – Consent Form	59
	ANNEXURE III- Proforma	62
	ANNEXURE IV- Randomization table	65
	ANNEXURE V- Master Chart	66

LIST OF TABLES

TABLE. NO.	DESCRIPTION	PAGE NO.
1.	Modified Behavioural Pain Scale	25
2.	Gender distribution	28
3.	Distribution of children in each group	29
4.	Distribution of pain score over time	30
5.	Baseline pain before giving injection in each group	31
6.	Comparison of pain score over time and intervention	32
7.	Comparison of parental VAS and intervention	34
8.	Correlation of MBPS and parental VAS	36
9.	Comparison of MBPS and gender	37

LIST OF FIGURES

FIGURE NO.	DESCRIPTION	PAGE NO.
1.	Visual Analog Scale	26
2.	Gender distribution	28
3.	Distribution of children in each group	29
4.	Distribution of pain score over time	30
5.	Comparison of pain score over time and intervention	33
6.	Comparison of pain score over time and intervention	33
7.	Comparison of parental VAS and intervention	35
8.	Comparison of parental VAS and intervention	35
9.	Comparison of MBPS and gender	38

INTRODUCTION

Vaccination is one of the most cost-effective interventions for control and prevention of diseases which can be achieved even without improving the overall socio-economic development of a country. The small-pox eradication is the greatest example and now the eradication of poliomyelitis from almost every country in the world. Expanded Program of Immunization which was launched in 1978 by the Government of India was the first organized way of vaccination in the country. There has been a significant reduction in mortality and morbidity due to pertussis, measles, diphtheria, poliomyelitis, and neonatal tetanus following the start of immunization programs in India.

To provide this protection in India, there is a group comprising of health planners and pediatricians, including the president of the Indian Academy of Pediatrics (IAP) as one of the members of this important committee. The committee recommended Government of India start new vaccines from time to time and based on the recommendations and feasibility, new vaccines be introduced in the program. The current immunization schedule recommended by the Indian Academy of Pediatrics recommends immunizations against about 14 diseases, which leads to the administration of about 17 to 27 injections by 2 years of age.[1]

For vaccination of children, guidelines specific to age are used which usually requires administration of about two to three doses by injection in a single visit. Therefore, we can say that in a pediatric setting, vaccination is one of the most frequently performed painful procedure.

In this world, no one should suffer from pain. This holds even for the infant who comes to us for immunization. Pain during immunization is a major cause of concern as it is the most common iatrogenic source of suffering for infants along with their parents, and the providers themselves.

All children have a pain memory and have the ability to anticipate painful procedures following which subsequent pain perception and response may get affected.[2] During an injection, the degree of lack of cooperation and behavioural distress observed often ranges from inconvenience to major management issues. Actions such as crying, yelling, and physical resistance creates further stress for parents, doctors, and other infants present. Going through such a distressful procedure often leads to apprehension and fear, and a vicious circle of fear, anxiety and pain may establish.[3-7] All these factors lead to vaccine dropouts and increased non-compliance on the part of children themselves, parents, and strikingly the provider too.

The positive impact of immunization on disease prevention and control is immense and therefore the pain associated can be considered as a necessary evil. Despite having the best of medical facilities and advancements in the field of pediatrics we still consider immunization pain as something inevitable, which every infant has to go through. Each infant now has to undergo a series of immunization procedures involving the administration of multiple vaccines in a single visit. Vaccinations contribute to majority of a healthy infant's initial life experiences with iatrogenic pain and therefore have the ability to play a important role in shaping the infant's pain during similar happenings in the future. With many new vaccines being

added to the schedule, this problem should not be ignored, or else we will be the ones effectively turning our children into 'human pin cushions'.[8]

Despite many experience-based studies on ways of pain reduction during immunization, evidence-based data on healthy vaccination practice in terms of the use of topical anaesthetic agents to alleviate the pain during vaccination is still lacking.

Currently, there is no established evidence in the literature especially in the Indian scenario on which modality provides the best outcome. Presently, both topical local anaesthetic (LA) spray and topical application of eutectic mixture of local anaesthetic (EMLA) cream are accepted intervention modalities as per the IAP guidebook on immunization 2018-2019.[1]

Because of this clinical equipoise, this trial is needed to compare the prospective effects of using LA spray and EMLA cream and encourage the usage of topical anaesthetics during immunization in the subset of the population of this region.

OBJECTIVES

To compare the pain reduction efficacy of using topical local anaesthetic spray with vapocoolant and EMLA cream during vaccination in children.

REVIEW OF LITERATURE

EPIDEMIOLOGY OF PAIN

During childhood, immunization is the most frequent medical procedure done which is painful. To counter the newly emerging infectious diseases, the development of more vaccines and their administration is anticipated.

New technology which includes controlled-release delivery systems and some new adjuvants are also being investigated to reduce the number of shots in a multidose vaccination schedule.[9] However, these methods are less likely to be available for use anytime soon. Despite having combination vaccines, the best of medical facilities, and advancements in the field of pediatrics we still consider immunization pain as something inevitable, which every infant has to go through and needles will continue to be the "negative" symbol of childhood immunisation.

Principles of pain relief

Pain alleviation is a fundamental human right. We can see the importance of pain relief in the principle "first do no harm". Therefore, the need to reduce this iatrogenic pain has been recognized by health care providers and the parents themselves. The concept of "atraumatic care" is being used as a basis for administering injections in infants and children. It can be defined as "the provision of therapeutic care in a way that minimizes physical and emotional distress to children and families".[10]

To protect a child's rights, the conditions which are required to be fulfilled include the use of minimally invasive treatment options, being able to provide informed consent, and least negative impact on the health of the child. These

prerequisites have been given by bioethicists as children themselves cannot be included in the decision-making process.[11]

All children have a pain memory and therefore the cumulative effect of pain and its consequences needs to be addressed. Pain is the highlight of any vaccination program among children as well as teenagers who are being selected for additional immunizations. And this creates an apprehension regarding the pain during immunization causing a lack of compliance and vaccine dropouts despite knowing its advantages and benefits.

PAIN EXPERIENCE IN CHILDREN

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Furthermore, pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life".[12]

It shows how pain experience and its impact differs from one individual to another especially at a young age when the pain response is being shaped. Just because infants cannot communicate verbally, its presence cannot be ignored. Young infants have greater pain responses from the same stimulus than adults because they have bigger receptive fields and do not have inhibitory controls of pain.[13]

The pain during immunization plays a significant part in the early life experiences of a child and hence can cause a potential impact on the child's pain perception in the future. As mentioned above child's perception of pain is much more than that of adults. There is one article in which the child compares the needle to an

animal.[14] Whenever a child is taken to a hospital, the only thing the child is concerned about is whether he/she will be receiving a shot.[15,16] All this shows how much a child is concerned regarding the pain and how frightening and painful the event must be for the child.

There are two separate events responsible for pain during the immunization, one is when skin and tissues are penetrated and the second is due to the delivery and deposition of injection contents in the tissue. The distress is more due to the apprehension itself rather than the physical injury caused during the procedure. The anticipatory fear responses induced before the actual procedure aggravate pain and distress encountered when it is actually being performed. And these anticipatory fear responses generated can be attributed to the planned nature of any immunization event.[17] A child does not get habituated to the pain over time as believed earlier, rather, conditioned anxiety response is generated immediately and manifested as a foreseeable fear.[18] Multiple elements determine the fear response of a child like cognitive development, environment, use of analgesia, parental behaviours, and the memory of previous similar experiences.[12,19]

Usually, younger children have a lesser pain threshold than older children. Exaggerated pain responses may be seen in children who are temperamentally more difficult to deal with. Gender has not been implicated as a factor determining the pain response. In general, males report less pain than females tend to do, but this is observed more in the adolescent age group.

Additionally, some factors have an effect on an infant's pain response while immunization is being carried out like the usage of analgesics and the environmental set-up. Multiple pain reduction strategies are recommended during immunization

which is in the form of physical, psychological, and even pharmacological interventions or a combination of these.

The usage of less painful formulations, positioning of the child in the mother's lap, stroking skin around the vaccination site and the sequence of giving less to more painful injection if there are multiple injections scheduled on the same day are a few of the physical interventions advised.[20] Similarly psychological interventions include techniques of distraction, breathing exercises, and cognitive behavioural therapy.[21] The various pharmacological interventions include the use of topical anaesthetic agents in the form of cream, gels, or spray, sweetening agents like sucrose, and breastfeeding while the procedure is being carried out.[22]

The amount of pain and distress during the process of immunization is also influenced by parental behaviour.[23] The behaviour which helps the child cope included engagement in non-procedural talks, distraction, humor. However, empathy, criticism, reassurance, apologies, and parental anxiety tend to increase the child's pain and distress. Since parents cannot be present in all instances of vaccination, even the health care provider should be aware of using these coping strategies to minimize distress. Parental concerns regarding the pain during immunization have also been expressed in terms of the willingness to pay to decrease the number of vaccinations given to the child.[24]

Long-term outcomes of pain

The pain during immunization has a long-lasting impact on the child including increased fear of future procedures in anticipation, reduced analgesic effects, an unusual fear of needles i.e., needle phobia.[25]

The distress and pain child experiences depend on how much the child remembers about the previous event. More negative memories amount to greater distress.[26,27,28] Just because there is no verbal reporting of the pain does not imply that there is no negative physiological consequence to the procedure.[19,29] Some studies have mentioned about the changes in future pain responses based on painful events in the infant period.[30,31]

Pretreatment of a painful procedure with some intervention prevented the aggravated pain response during subsequent vaccination. If the pain is not managed adequately initially, then during future procedures there will be increased requirements of analgesia.[32]

Success of any procedure especially in pediatric age group largely depends on the cooperation of the child which is determined by the distress and pain which the child experiences during the procedure and also on the anticipatory fear response to those procedures. Therefore, use of analgesia can help in completion of these procedures with ease and the chances of procedure failure secondary to distress are less likely.[33,34]

In about 10% of the population, a negative consequence of untreated injection pain is observed and as per the Diagnostic and Statistical Manual of Mental Disorders known as needle phobia.[25,35] It can be defined as an unusual fear of needles. It usually develops during childhood after a negative experience in a clinical setting. Avoidance behaviour towards procedures can be seen in these individuals and it might result in injuries or trauma too. There is a development of fear towards people, events, and objects associated with needles. Even if the diagnostic criteria are not met in some children, they do exhibit anticipatory anxiety and fear regarding vaccinations.

Consequently, due to these fears, children and as well as their parents avoid seeking medical help when required. They avoid regular checkups, immunizations, dental procedures, and even their compliance to treatment involving needles is affected. And just because of needle phobia they are at a higher risk than the usual population for morbidity and mortality.

Non-compliance to Immunization Schedules

In about 25% of children, vaccination schedules are not followed. The pain associated with immunization has been considered as a significant determinant for adherence to the vaccination schedule.[36,37,38] Apprehension of children crying or receiving multiple injections in the same setting on the part of parents is also responsible for this delay.[39,40] Physicians are also responsible for non-adherence to immunization schedules as they avoid giving elective immunization or giving multiple shots at a time. All these factors causing incomplete immunization make the child and society vulnerable to the resurgence of infectious diseases and failure of the immunization program[38,41]. As we can see that the success of any vaccination program largely depends on compliance to the schedule, we should focus more on alleviating this injection pain.

CURRENT PRACTICES TO ALLEVIATE PAIN

There have been multiple systemic reviews[20-22] which mention about various evidence-based interventions available for reducing injection pain associated with immunization. Despite of usage guidelines developed[15,42], the application of these practices has been suboptimal. It has been found that the proposed usage of pain management strategies is rarely being used in clinical practice. In one study, only

about 1 % children were being subjected to topical anaesthetics in a study despite of its proven effectiveness[22].

It has already been proven that rapid intramuscular injection without aspiration causes less pain and is a cost-free technique of pain alleviation[43]. Contrary to this, about two-third physicians reported that they still practice injection with aspiration[44].

Holding and distraction techniques have been proved effective in reducing pain and about 70-80% mothers do follow them, but additional detailed studies are required to know whether there was any element of restraining involved or was it actually comforting[20,21].

One study shows that the usage of psychological and pain-alleviating measures helped in reducing the recall of painful experience during immunization 6 months post the event[29]. Therefore, establishing the fact that consistent pain management is an effective way to deal with children subjected to repeated medical procedures.

The development of fear depends on multiple factors like temperament, cognitive levels, previous experience, environment and not only physical pain[45,46]. Hence the use of analgesia alone will not suffice for pain management and a comprehensive approach is required that takes all the factors into consideration. Basic principles for management of immunization pain includes pre-procedural preparation of the child, effective pain management intervention, appropriate parental behaviour and a positive surrounding.

OBSTACLES WHILE PRACTICING PAIN ALLEVIATION

During immunization, suboptimal usage of pain prevention interventions can be due to paucity of awareness regarding pain, about the interventions and the outlooks regarding the procedural pain[47,48]. There are several myths held regarding painful procedures in children.

Lack of Awareness Regarding Pain Among Parents

The most common reason given by parents for not managing the pain during vaccination is the lack of awareness, insufficient information about the available interventions[49]. They also report their concerns regarding their effectiveness, adverse effects and interference with the immunization process. It has been found that doctor's advice regarding these interventions is significant in determining parental usage of these distress management strategies. But most of the parents report that routinely they are not advised about pain control strategies by their doctors. And even the physicians have accepted the fact that unless and until they are requested about pain control by the parents, they do not use or advice regarding the same[49]. More commonly they counsel them regarding the adverse effects like fever and how to deal with them.

Parents not being able to recognize that their child is suffering or experiencing pain is another issue faced[50]. There are many signs to indicate the presence of pain. Responses such as crying, grimace, intense body movements like writhing can be seen in children who cannot express it verbally. But since these cues exist during both presence or absence of pain, sometimes parents or even healthcare providers tend to ignore them. Therefore, due to existence of such ambiguous signs of distress, additional efforts to alleviate all the sources of pain are recommended. On the other

hand, in older children we can obtain self-report and the behavioural response to pain will be specific unlike in preverbal children where it is nonspecific. However, in all age groups there will be physiological and biochemical responses obtained in response to pain. But it can only be evaluated and monitored in limited settings.

Hence, we can infer that parents require training and education in order to identify pain in their children. They should be provided with written supplements or demonstrations to educate them about pain reduction techniques. Parents should also be taught about the behaviours which promote coping and what causes distress, so that parents can manage the pain efficiently.

We should even focus on preparing children for scheduled vaccinations[26]. In this way children can anticipate their response to pain and plan how they want to deal with it. This early preparation promotes trust and results in enhanced cooperation[51] during the procedure and therefore saves the time which used to be utilized in preparing the child just before the injection. There is no optimal timing for preparing the child regarding the injection[52]. But as per previous studies, school aged children should ideally be informed a day prior and toddlers and infants to be prepared just prior to the procedure[52,53]. They should be informed about the steps of procedure; how will it feel like and what can they do to minimize the pain or distress[52,54]. All these explanations to be given appropriately as per age.

Misconceptions Among Health Care Providers

Despite of being a planned event with enough time to plan pain management, the health care providers mostly hold a “get it over with” attitude and therefore this viewpoint does not resolve the infant’s apprehension of experiencing pain[55]. Physicians claim that usage of topical analgesia is not feasible due to the cost and

time involved[49]. They also express regarding parental competence which is required for proper usage of these agents. This report by the health care providers is contrary to the study which mentioned regarding the willingness to pay among parents so as to reduce the pain during immunization[49,56]. And parents have reported that they are ready to apply topical anaesthetics at home themselves to prevent delays at doctor's office[57,58].

Health care workers tend to disregard the benefits of using topical local anaesthetics because of their inability to acknowledge the presence of pain, inability to discriminate between the responses of children to pain, misconception of these agents interfering with the effectiveness of vaccine and because of not being able to value these agents as they do not alleviate the suffering completely.

The effectiveness of topically applied local anaesthetics is questioned because its usage does not ensure complete alleviation of pain. There is strong evidence proving the pain reducing capabilities of the topical local anaesthetics, but no evidence to prove complete elimination of pain. Therefore, doctors are sometimes not very much interested to deal with the vaccination pain as it requires more than just local application of analgesic agents.

We need to adopt an infant-focused attitude which identifies and reduces agony and hence allow us to have an immunization system which involves distress free children, parents and health workers. If we practice pain management at each and every step, children will learn how to deal with pain, how to be compliant and cooperative and this will also strengthen their trust in health care facility.

Social Barriers in Practicing Pain Management

Due to the prevalent cultural attitudes towards pain which states painful experiences are a part of life and therefore helps infants grow as fitter and healthier adults[59], parents usually do not request for pain relief and health workers might not provide it. Parents may in fact worry about the pain but underrate that concern because of these attitudes and fears of negative repercussion for their children if they complain about pain and then feel enormous guilt or betrayal for allowing their children to suffer[60].

Some people just like they have accepted the chances of adverse event occurring as an unavoidable consequence, similarly they have accepted that the pain during vaccination is the price for attaining worldwide immunity and disease elimination[61].

There is a strong need to change the attitudes of vaccinator as well as the society towards immunization pain. We need to emphasize the long-term adverse consequences of this so called short lived painful experience during injection and also that it could be avoided with ease as a part of ethical medical practice. We have a chance to attain better health results in terms of protection from infectious diseases without any pain for children undergoing vaccination indicating good quality of life. This will be aided by our increasing scientific awareness regarding the harmful effects of pain and the increasing availability of various pain preventing strategies.

STUDIES ON INJECTION PAIN AND ITS PREVENTION

A study was done in 1991 by Maikler et al[2], in which sixty infants undergoing routine DPT vaccination were studied. Before injection, infants were either subjected to a skin refrigerant i.e., Frigiderm or to compressed air as per randomization. Pain response behaviour was recorded during and one minute after injection and was scored accordingly based on expressions of face, crying and bodily gestures. The results showed that that there was less pain in infants which were subjected to the refrigerant spray. It also showed that the children to whom refrigerant was applied showed less startling when pricked and the time taken for child to cry was longer in that group. The study also revealed that older infants had pain expression for a lesser duration than the younger infants when pricked. (b)

In 1993, a randomized controlled trial was done by Taddio et al[57] to determine the efficiency of EMLA cream (5%) in reducing pain during DPT vaccination in infants. Forty-nine infants were subjected to EMLA and forty-seven received placebo. MBPS was used to score the infants at two time points i.e., one at baseline and one post-procedural score. The mean difference of the before and after vaccination score along with latency to first cry and total crying time in the two groups was noted. The study showed that the difference in the pain score was much lesser for the group which received EMLA. It also showed that the it took much longer time to cry for the children who received EMLA and also that the total crying time for the EMLA group was much shorter. But the study also showed that about 90% of the infants which received EMLA had skin blanching following its application.

A survey was done in 1995 by Woodin et al[8] to know the perspective of a parents as well as health care provider in regard to children being subjected to

multiple injections during vaccination. It showed that that about 31% parents were even concerned about their children receiving a single injection. About 41% parents were concerned about their child receiving three shots. Contrary to as expected, about 60% physicians were concerned about administering three injections. It increased to 80% when asked about four injections. Therefore, it was concluded that physicians were much more apprehensive regarding the administration of multiple injections to children in a single visit, whereas parents preferred this practice. Pain was the single most important concern for both physicians as well as parents.

A study by Abbott et al[62] in 1995 aimed to assess refrigerant anaesthetic spray's efficiency in alleviating pain during vaccination. The subjects were assigned to three different groups and received either refrigerant spray, placebo spray or no spray. Four-point visual analogue scale was used for subjective determination of the pain score. The study showed that using an intervention like a refrigerant spray was an effective way to minimize pain. It also revealed that parents are not able to determine the pain experience of their child accurately. This study showed a result contrary to the existing literature of older infants reporting more distress than younger ones. Since the pain was lesser in placebo spray group than the control, this study also proved the potency of placebo sprays in alleviating distress and hence promote development of cognitive pain strategies. There was no correlation of parental anxiety and pain experiences of children as suggested in earlier literature.

In 1997, a study by Reis et al[63] was done showing equal efficacy of vapocoolant spray and EMLA (2.5%) cream in pain minimization during immunization. In this study combined interventions were used. There were three groups i.e., vapocoolant with distraction, cream with distraction and distraction alone

as control. Observational scale of behavioural distress was used to score the children along with which cry duration was also noted. VAS scoring was done by child, parent, health worker and the investigator. All the pain scores and cry duration in EMLA and vapocoolant group were noted to be similar and better than the control alone. It was also concluded that vapocoolants are a faster acting and a more economic tool for pain alleviation with same efficiency as EMLA cream.

Lindh et al[64] did a study in 2003 to assess the pain reducing ability of EMLA cream and oral glucose. It was a randomized controlled trial having two groups with EMLA with oral glucose in one and placebo cream and water in another. Parents and healthcare workers scored the pain response behaviour on VAS. Physiological measurements like heart rate, heart rate variability and ECG changes were also recorded pre and post injection. Latency to first cry and total duration of cry was also noted. All the scores and parameters in the study concluded that EMLA and glucose was an effective pain management strategy during vaccination.

A study similar to the above-mentioned study was conducted in India in 2011 by Dipankar et al[65]. The study assessed the pain reducing ability of oral sucrose in infants undergoing DPT immunization. The results showed that oral sucrose had a statistically significant pain reducing ability when compared to sterile water.

Reis et al[66] in 2003 conducted one more study to assess the effectiveness of combination strategies in reducing immunization pain in infants receiving multiple injections in a single setting. Intervention group consisted usage of oral sucrose, oral tactile stimulation and positioning technique. Control did not use either of these. Infants which were included were receiving four shots in a single setting. Videotaping was done and crying time, heart rate, parental preference and ease of administration of

the injection for nursing staff was assessed. Cry duration was found to be much lesser in intervention group. Parents showed their preference towards the usage of same techniques in the intervention group. For nurses the ease to perform administration of vaccination in the intervention group was comparable to control group.

In 2007, an evidence-based review[15] was done and recommendations which were given on pain reduction during pediatric immunization also showed concern regarding inadequate information available for addressing distress associated with immunization. This review covered various aspects of immunization starting from how pain associated is a source of stress for infants, parents and the vaccinators. Then it mentioned about the importance of preparing a child prior to injection. About how the site of injection varies with age. Length of the needle also plays a role in pain determination with longer needles causing less pain and reaction. The article mentions about the parental behaviour and its impact on child's pain experience. Excessive reassurance, apologies tend to aggravate the pain whereas humor, distraction reduce it. The efficacy of these techniques varies with multiple factors like age, cognitive level, environment. Usage of pharmacological interventions has also been described like use of oral sweeteners, various topical anaesthetic agents. Techniques of administering the injection also play a role. Parental preference of multiple injection in same setting has also been mentioned about. The need for new research in order to address these concerns regarding immunization pain has been expressed in this review.

In 2007 Taddio et al[49] conducted a survey reporting suboptimal usage of pain management strategies. About 58% of the pediatricians who responded reported they rarely or never used analgesic agent during the procedure of immunization. During

the injection EMLA was the most frequently used agent if used whereas paracetamol and ibuprofen were the most commonly used drugs in the post injection phase. Therefore, it was concluded that strategies to increase awareness regarding the harmful effects of pain and intervention for minimizing it are needed.

There was one study conducted by Cohen et al[67] in 2008 which was contrary to all the studies as it showed that vapocoolants are not effective in reducing injection pain. Study involved self-reporting of pain by children after they were subjected to the intervention or control as per randomization. The report suggested that there was a greater increase from baseline pain when the child was subjected to vapocoolant alone when compared to children in a typical care environment. Even the reports given by the healthcare workers were suggestive of same. This was attributed to the cold sensation following spray which could increase the pain response. Inadequate distraction from the procedure could also result in this way. Other reasons for such results could be because of a small sample size. Limitations of the study included non-usage of videotaping and non-homogenous nature of the samples included.

A systemic review and meta-analysis were done in both adults and children by Vibhuti Shah et al[68] in 2015. The various pharmacological and combined interventions to reduce injection pain were compared. The use of topical anaesthetic agents proved to be beneficial in reducing the pain scores and self-reported pain scores by adults. The use of vapocoolant was beneficial in adults but not in children. There were no benefits observed on using acetaminophen or ibuprofen .[21]

A study was done by Riyadh Firdaus, et al[69] in 2018 to compare vapocoolant spray and EMLA cream in reducing pain during spinal injections. It showed that both

lowered the pain but there was no difference in pain lowering ability when the two interventions were compared.

A survey conducted in Victoria by Harrison et al[70] questioned regarding the pain-relieving measures taken during immunization. It had nearly 125 respondents. Only about 15% respondents agreed to the fact that they had a policy regarding pain management during immunization. About 76% respondents stated that distraction strategies were used often. Breast feeding during vaccination was not used a measure for pain alleviation as per 45% respondents. They also reported that sweet tasting solutions or topical anaesthetic agents were almost never used.

Recently in 2015, a prospective, randomized controlled trial was conducted in Turkey by Sahiner et al[71]. The effectiveness of combined stimulation of external cold and vibration was assessed during vaccination. The stimulation was provided using a device called Buzzy. Children were randomized into two groups: experimental (external cold and Buzzy) and control (no intervention). The pain and anxiety levels of the children were assessed using the Wong-Baker FACES scale and Children Fear Scale. It showed that the intervention group had significantly lower level of pain and anxiety experienced.

Currently there is no established evidence in the literature especially in the Indian scenario on which modality provides the best outcome. Presently, both topical anaesthetic spray and EMLA cream are accepted intervention modalities as per IAP guidebook on immunisation 2018-2019[1].

METHODOLOGY

This study was done from September 2020 to September 2021 in the Immunization Clinic of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre (MRC), Belagavi and Rukmini Nagar Urban Health Centre, Belagavi.

Study Design:

Randomized, open-label, parallel-group.

Study duration and study period:

One year duration from September 2020 to September 2021.

Place:

Study was done in the Immunization Clinic, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi and Rukmini Nagar Urban Health Centre, Belagavi.

Inclusion Criteria:

All healthy infants of age group 9-11 weeks who were brought for immunization with 2nd dose of Liquid Pentavalent Vaccine.

Exclusion Criteria:

1) Infants receiving treatment with methaemoglobin-inducing agents.
2) Infants on medications which can alter pain perception and response.
3) Neurologically depressed infants due to any condition.

4) Infant with known allergy to any injection constituent or following any previous dose administration.

5) History of reaction following application of topical anaesthetic agent.

Sample Size:

The sample size was obtained through G*Power software. Study had three groups and data was collected at 3 different time points (before, after 1 minute, after 5 minutes).

On assumption of a small effect size of 0.1, level of significance as 5%, power 85%, non-sphericity correction ε taken as 1 and by assumption of correlation present between repeated measures as 0.5, a total sample size of 228 was obtained in which each group comprised of 76 subjects.

Ethical Clearance:

Before the start of the study, it was approved by the Institutional Ethics Committee. (Annexure I)

This trial was registered in CTRI with this number **CTRI/2021/05/033426.**

Informed Consent:

Parents of the children brought for immunization on fulfilling the eligibility criteria were explained regarding the nature of the trial. And, before enrolment of a subject written informed consent was taken. (Annexure II)

Protocol:

Once the child was brought to the immunization clinic and if the child fulfilled the eligibility criteria, he/she was enrolled into the study after taking the consent. Relevant data was obtained from the parents and recorded in a structured proforma. (Annexure III)

The enrolled subjects were randomised into any of the three groups:

Randomisation was done by a computer-generated sequence. (Annexure IV)

Control Group: Infants who did not receive any form of local anaesthesia

Intervention Group:

Group A: Infants on whom EMLA cream was applied.

Group B: Infants who were given topical LA spray with vapocoolant.

The procedure of vaccination was conducted by single trained personnel. The vaccine was given intramuscularly into the anterolateral aspect of thigh using 25 G, 1-inch length needle inserted at 90 degrees angle after preparing the skin while the infant was lying flat on the examination bed.

Topical local anaesthetic spray with vapocoolant was containing benzocaine 0.36% along with polyvinyl polymer 2.52% in a propellant solvent. It was sprayed 10 seconds before the administration of injection over the site of injection.

2.5 grams of EMLA cream that is Lidocaine and Prilocaine 2.5% in a water miscible base was applied about an hour before the injection and was kept covered with occlusive dressing.

In both groups, the data was recorded by a trained pediatric post graduate resident posted in the OPD and was blinded for outcome of the study

Outcome measures:

a) The pain scores were given as per Modified Behavioural Pain Scale mentioned below. The 10-point MBPS assesses 3 behavioural components (facial expression, movements, and cry) as an indication of a child's experience of pain. Total score is the sum of scores in each parameter. Maximum score of 10 indicates worst pain experience and the least possible score of 0 indicates no pain. It was recorded before the injection and at 1 and 5 minutes after the injection by observer

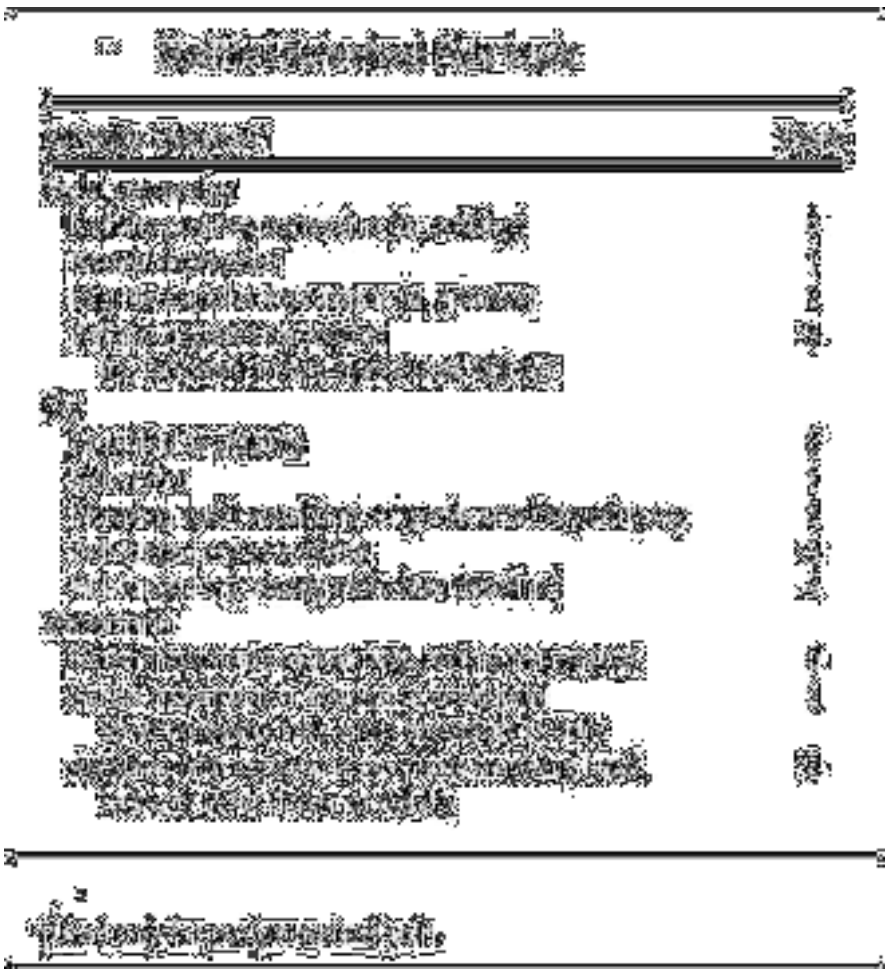

Table No.1: Modified Behavioural Pain Scale.

b) Parents had to rate the infant's pain experience during vaccination on a Visual Analog Scale (VAS) mentioned below. It is a validated, subjective measure for acute pain where zero is designated as "no pain" and 10 the "worst possible pain".

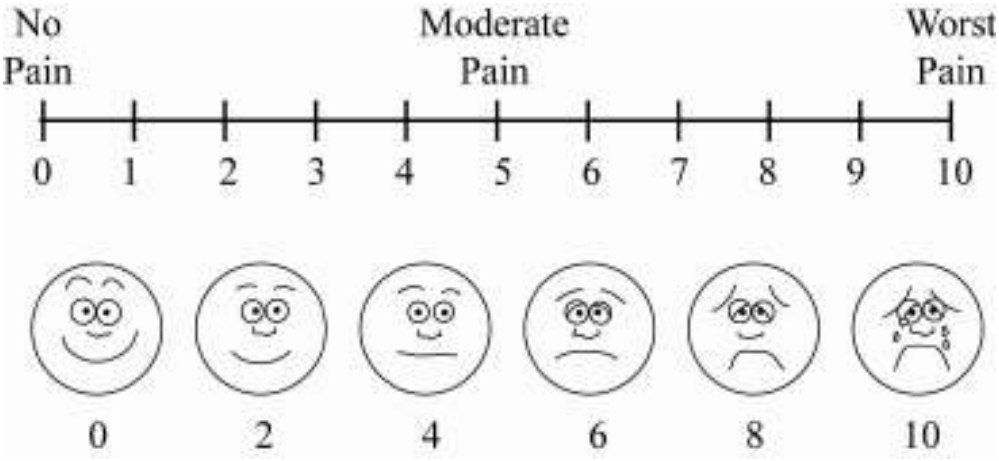

Figure No.1: Visual Analog Scale

Data analysis:

Statistical software R version 4.1.1 and Microsoft Excel was used to analyze the data obtained. Continuous variables were represented by mean± SD/median and categorical variables represented by frequency. To check the normality of variables, Shapiro-Wilk's test was used. Kruskal-Wallis test was used to compare the distribution of continuous variables over intervention. To check the association between two categorical variables, Chi-square test was used. MBPS over time was compared using Friedman's test. A p-value of less than or equal to 0.05 indicates that the data is statistically significant.

RESULTS

RESULTS OF COMPARING THE EFFICACY OF TOPICAL LOCAL ANAESTHETIC SPRAY WITH VAPOCOOLANT VERSUS EMLA CREAM FOR PAIN ALLEVIATION IN INFANTS DURING VACCINATION

A Randomized controlled trial was done to study the efficacy of topical LA spray with vapocoolant versus EMLA cream for pain alleviation in infants during vaccination. It was conducted over a period of 1 year from September 2020 to September 2021.

A total of 228 samples were collected, which were divided in to three groups of EMLA cream, local anaesthetic spray and control according to random number table and were scored as per the pain scales by observer and parents.

Tables – 8

Figures - 8

1. GENDER DISTRIBUTION

Out of 228 children who completed the study, 127 (55.7%) were male.

Table No.2: Gender Distribution

Gender	Frequency	Percent
FEMALE	101	44.3
MALE	127	55.7
Total	**228**	**100.0**

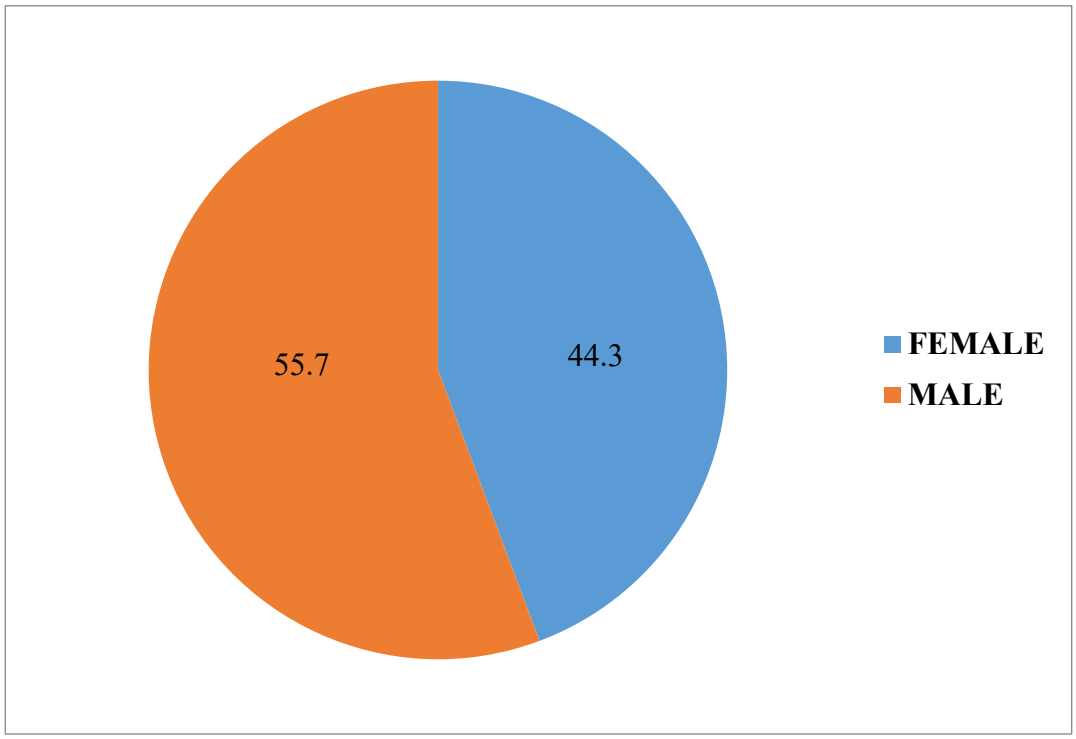

Figure No.2: Gender Distribution

2. DISTRIBUTION OF CHILDREN IN EACH GROUP.

The children were randomly divided into three groups of 76 each

Table No.3: Distribution of children in each group

Intervention	Frequency
CONTROL	76
GROUP-A (EMLA CREAM)	76
GROUP-B (LA SPRAY)	76
Total	**228**

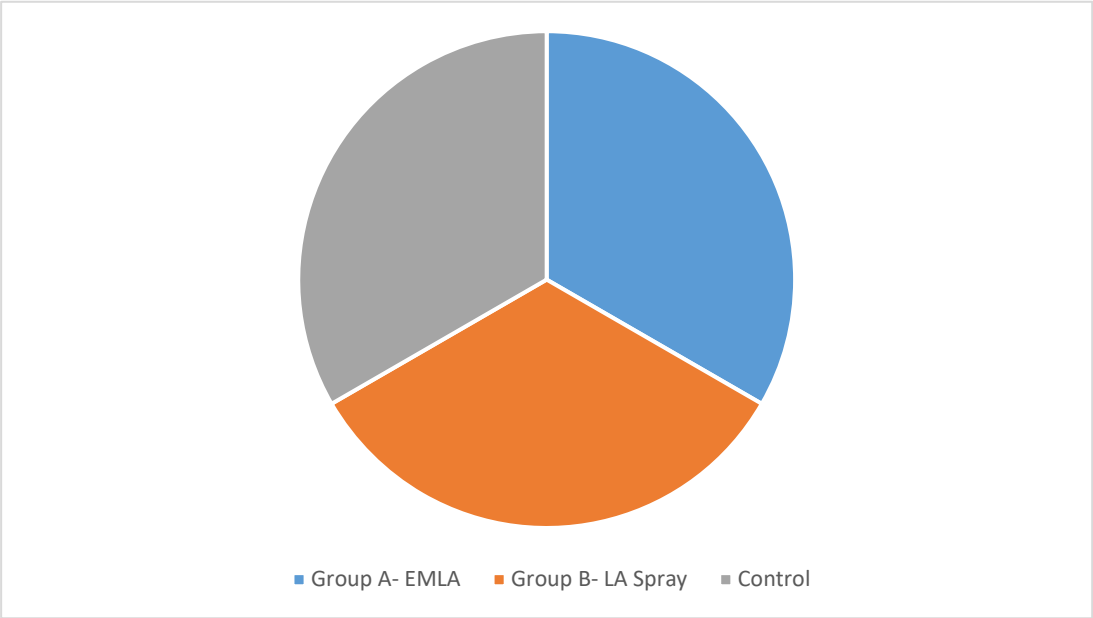

Figure No.3: Distribution of children in each group

3. DISTRIBUTION OF PAIN SCORE OVER TIME

Highest pain scores irrespective of the group, as per MBPS were recorded at 1 minute post injection (6.32±1.46) when compared to score at baseline (1.80±0.79) and at 5 minutes post injection (2.86±1.46).

Table No.4: Distribution of pain scores over time

Pain Scores	**Mean** ± SD
MBPS-0	1.80±0.79
MBPS-1 min	6.32±1.46
MBPS-5 min	2.86±1.46

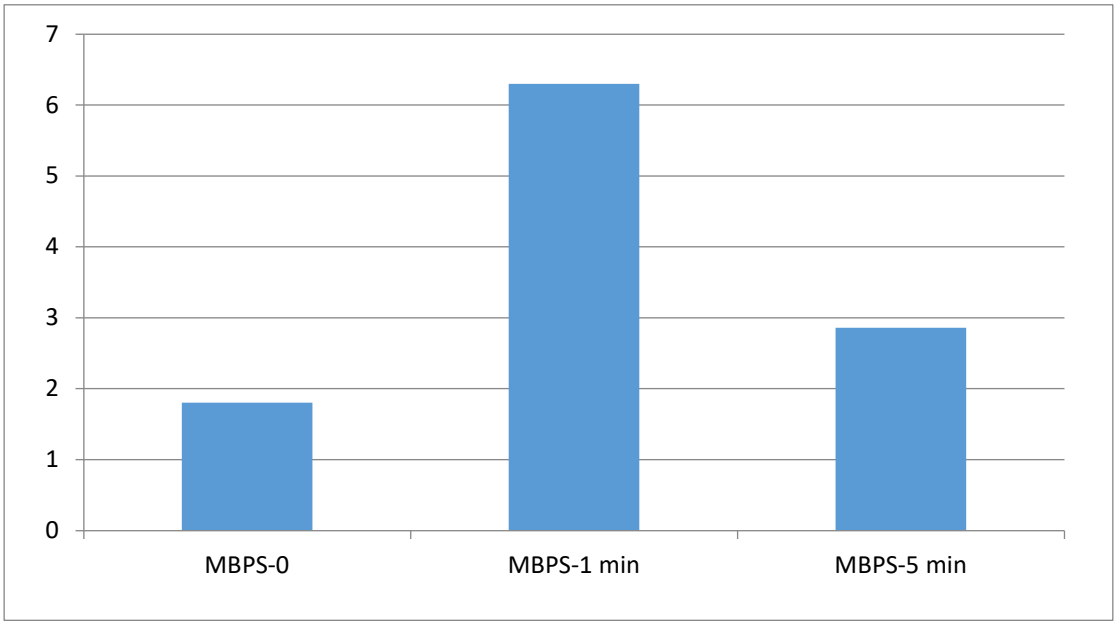

Figure No.4: Distribution of pain scores over time

4. BASELINE PAIN SCORE BEFORE GIVING INJECTION

Baseline pain score as per MBPS in each group i.e., EMLA cream (1.74±0.77), LA spray (1.84±0.8) and control (1.82±0.81) were similar before giving the injection with no statistically significant difference ($p>0.05$) between the groups. The minimum and maximum score was 1 and 3 respectively in all groups.

Table No.5: Baseline pain score before giving injection

	Intervention			**Total**	**p-value**
	GROUP-A (EMLA CREAM)	**GROUP-B (LA SPRAY)**	**Control**		
MBPS at 0 min	1.74±0.77 2 (1, 3)	1.84±0.8 2 (1, 3)	1.82±0.81 2 (1, 3)	1.8±0.79 2 (1, 3)	0.711^{KW}

5. COMPARING PAIN SCORES OVER TIME AND INTERVENTION

Table No.6: Comparison of pain scores over time and intervention.

		Intervention			Total	p-value
		GROUP-A (EMLA CREAM)	GROUP-B (LA SPRAY)	Control		
MBPS	0 min	1.74±0.77 2 (1, 3)	1.84±0.8 2 (1, 3)	1.82±0.81 2 (1, 3)	1.8±0.79 2 (1, 3)	0.711^{KW}
	1 min	6.22±1.14 6 (4, 8)	5.11±1.1 5 (3, 7)	7.62±0.89 8 (6, 9)	6.32±1.47 6 (3, 9)	<0.0001*^{KW}
	5 min	2.82±0.78 3 (2, 4)	2.79±0.79 3 (2, 4)	2.96±0.77 3 (2, 4)	2.86±0.78 3 (2, 4)	0.3288^{KW}
p-value		<0.0001*^{F}	<0.0001*^{F}	<0.0001*^{F}	<0.0001*^{F}	-

The mean MBPS score at 1 minute was least in the group using topical local anaesthetic spray with vapocoolant (5.11±1.1) followed by EMLA group (6.22±1.14) whereas control group (7.62±0.89) exhibited the maximum pain score values This distribution of pain score at 1 minute between the interventions was statistically significant by KW test. Dunn's test for post-hoc analysis shows significant difference in the distribution of pain scores at 1 minute between every pair of intervention A-B (p-value: <0.0001*), A-Control (p-value: <0.0001*) and B-Control (p-value: <0.0001*)

The difference in the distribution of MBPS pain scores at 0 and 5 minutes between the interventions by KW test was statistically insignificant.

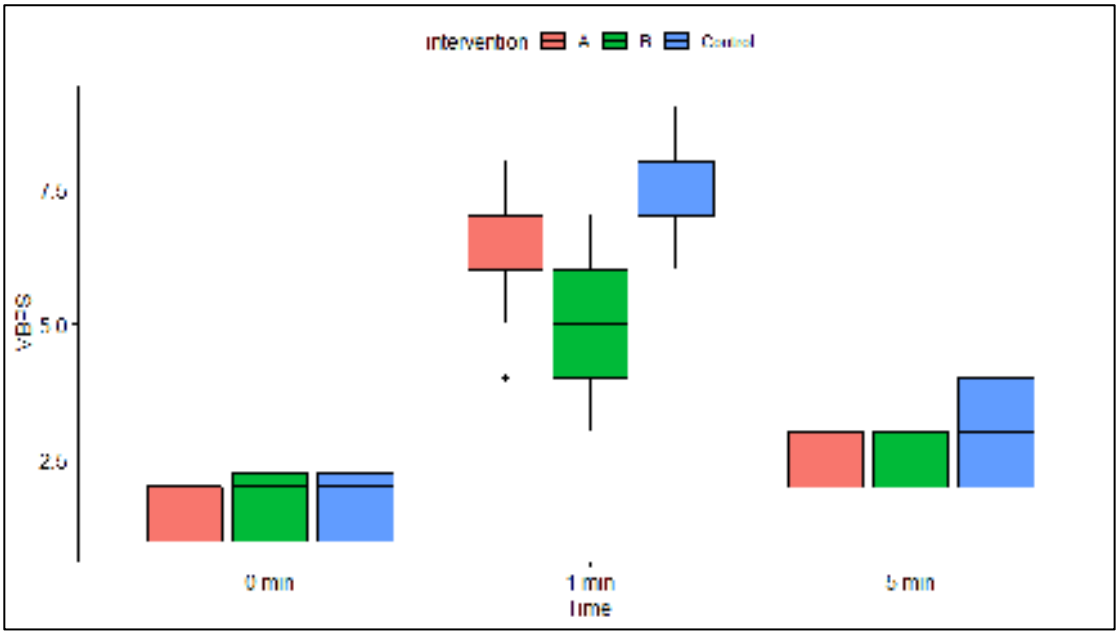

Figure No.5: Comparison of pain score over time and intervention.

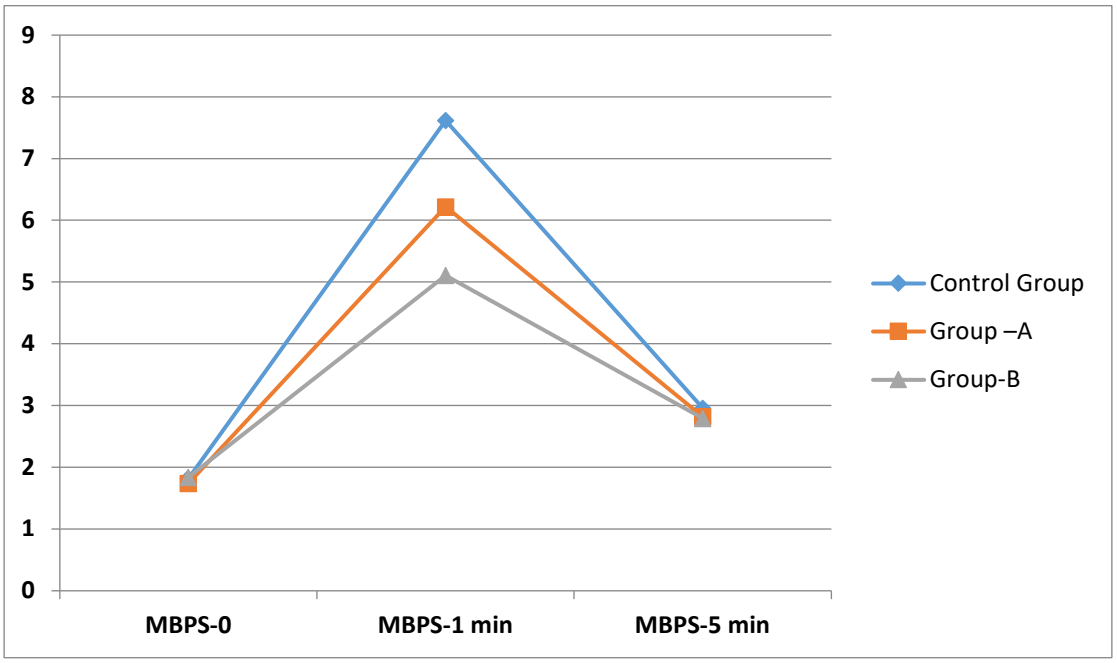

Figure No.6: Comparison of pain score over time and intervention.

6. COMPARISON OF PARENTAL VAS SCORE AND INTERVENTION

Table No.7: Comparison of parental VAS and intervention.

	Intervention			Total	p-value
	GROUP-A (EMLA CREAM)	GROUP-B (LA SPRAY)	Control		
Parental VAS	4.5±1.31 4.5 (2, 7)	3.66±1.66 4 (0, 8)	5.82±2.56 5 (2, 10)	4.66±2.11 4 (0, 10)	<0.0001*KW

The mean VAS score is least in group using topical local anaesthetic spray with vapocoolant (3.66±1.66) followed by EMLA group (4.5±1.31) whereas control group (5.82±2.56) exhibited the maximum pain score values as per parents.

There is significant difference in the distribution of parental VAS between interventions by KW test. Dunn's test used for post-hoc analysis and it is observed that, there is significant difference in the distribution of parental VAS between every pair of intervention used A-B (p-value: 0.0066*), A-Control (p-value: 0.0134*) and B-Control (p-value: <0.00001*).

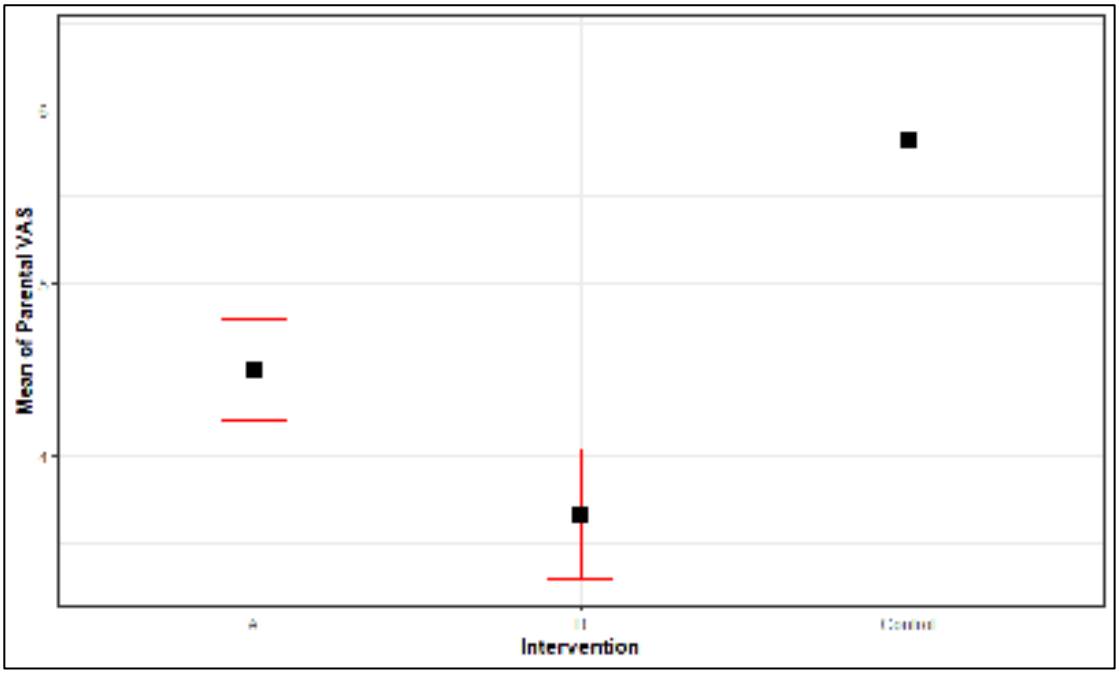

Figure No.7: Comparison of parental VAS and intervention.

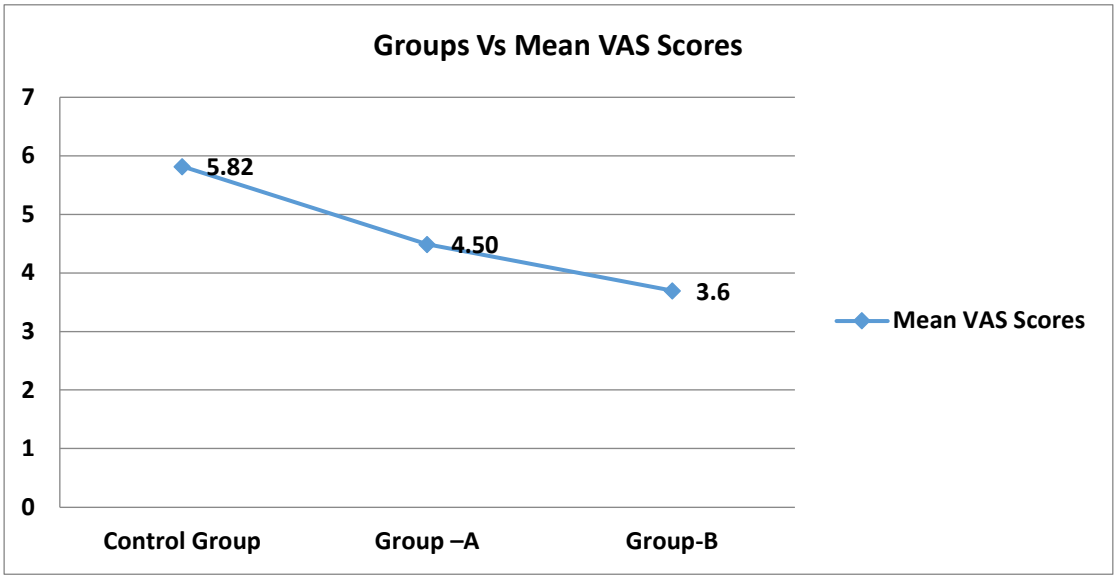

Figure No.8: Comparison of parental VAS and intervention.

7. CORRELATION OF MBPS AND PARENTAL VAS

Below table gives the correlation between MBPS at different time point and parental VAS within each group.

Table No.8: Correlation of MBPS and parental VAS with respect to group and time.

	Intervention		
	GROUP-A (EMLA CREAM)	**GROUP-B (LA SPRAY)**	**Control**
MBPS at 0 min	ρ = -0.0592 p-value: 0.6114	ρ = 0.01706 p-value: 0.8836	ρ = -0.03761 p-value: 0.747
MBPS at 1 min	ρ = 0.04367 p-value: 0.708	**ρ = 0.31784** p-value: **0.005143***	ρ = -0.19569 p-value: 0.09023
MBPS at 5 min	ρ = 0.04487 p-value: 0.7003	ρ = 0.14416 p-value: 0.2141	ρ = 0.02279 p-value: 0.845

From Spearman's correlation, there is moderate positive correlation present between MBPS at 1 minute and parental VAS in intervention group using local anaesthetic spray.

8. COMPARISON OF PAIN SCORE AND GENDER

Below table gives the comparison between MBPS at different time point and gender over time.

Table No. 9: Comparison of MBPS and gender.

		Gender		Total	p-value
		Males	**Females**		
MBPS	**0 min**	1.83±0.79 2 (1, 3)	1.75±0.79 2 (1, 3)	1.8±0.79 2 (1, 3)	0.4217^{KW}
	1 min	6.24±1.45 6 (3, 9)	6.42±1.49 7 (3, 9)	6.32±1.47 6 (3, 9)	0.3453^{KW}
	5 min	2.81±0.73 3 (2, 4)	2.91±0.84 3 (2, 4)	2.86±0.78 3 (2, 4)	0.4164^{KW}
p-value		$<0.0001^{*F}$	$<0.0001^{*F}$	$<0.0001^{*F}$	-

There is no difference in the distribution of MBPS at 0-minute, 1 minute and 5 minutes between the genders by KW test.

By Friedman's test, there is significant difference in the MBPS over time within each gender category. Wilcoxon's test used for post-hoc analysis and there is significant difference between every pair of time (p-value: <0.00001*) within each gender category.

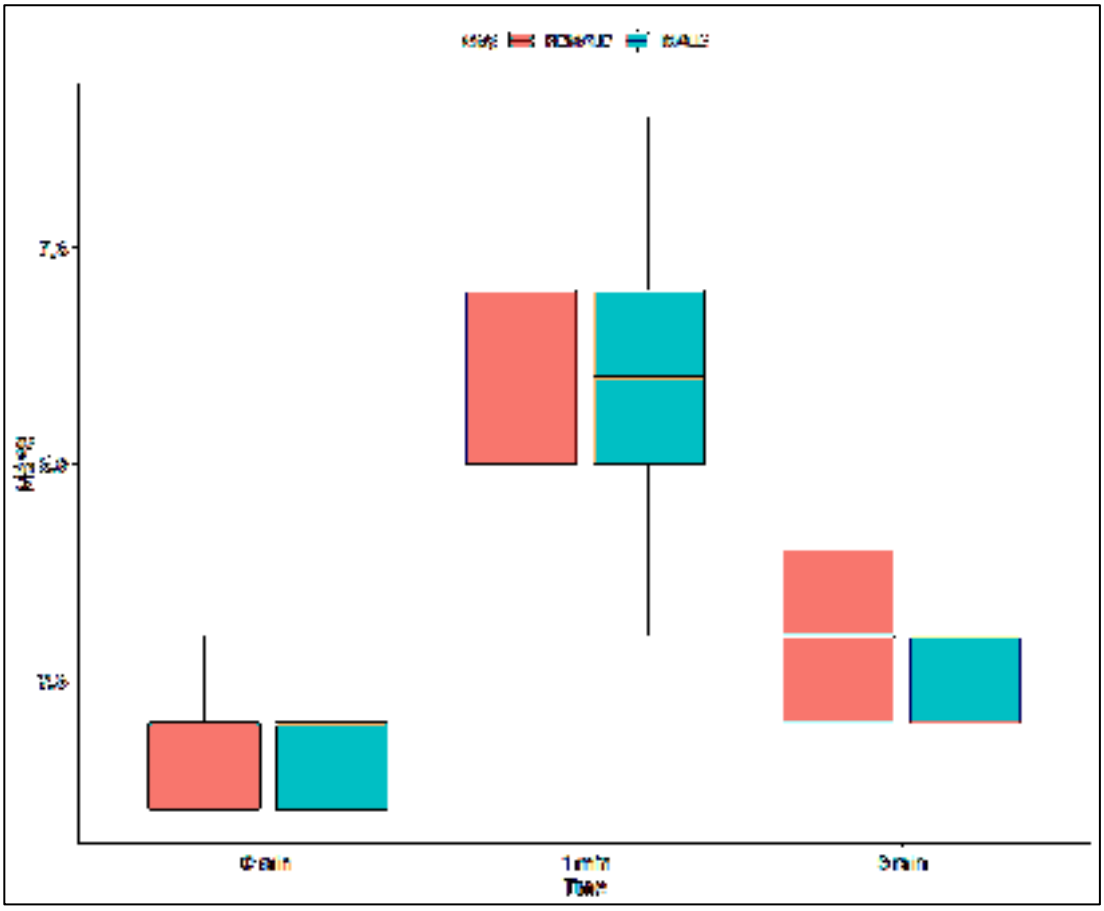

Figure No.9: Comparison of MBPS and gender.

DISCUSSION

Routine childhood vaccination is a necessary aspect of healthcare of children and its importance in eradication and controlling the emergence of diseases has been known for years. Despite its key role, immunization is either refused or delayed due to multiple factors. One of the most important cause for this is the injection pain during vaccination and the apprehension associated with it. This leads to non-compliance on the part of children, parents and at many times providers too.

There have been multiple studies conducted to find out new ways of dealing with this aspect of immunization. Various physical, psychological, pharmacologic and combined interventions have also been described. But despite of the frequency with which vaccinations are performed and the amount of distress and apprehension it provokes in children, parents and the physicians, we see a lack of evidence-based information on multiple facets related to ideal vaccination practice.

Currently there is no established evidence in the literature especially in the Indian scenario on which modality provides the best outcome. Presently, both topical anaesthetic spray and EMLA cream are accepted intervention modalities for pain management.

Our study aimed to compare the efficacy of topical local anaesthetic (LA) spray with vapocoolant versus EMLA cream for pain alleviation and encourage the usage of topical anaesthetics during immunization in the subset of population of this region.

The study was done in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi and Rukmini Nagar Urban Health Centre, Belagavi from

September 2020 to September 2021. It was a randomized controlled trial consisting of 228 children in the age group of 9 to 11 weeks brought for immunization with 2nd dose of liquid pentavalent vaccine.

The children were randomized using random number table into three groups with 76 participants in each group. According to the group randomized, the study subjects were either given EMLA cream or LA spray or if the child was in control group, then routine immunization practice was followed and no form of local anaesthesia was given.

The two modalities of pain management were compared in this study. Modified Behavioural Pain Scale (MBPS) was used to score the pain experienced at baseline, at 1 minute post injection and at 5 minutes post injection. The 10-point MBPS assesses 3 behavioural components (facial expression, movements, and cry) as an indication of a child's experience of pain. Total score is the sum of scores in each parameter. Maximum score of 10 indicates worst pain experience and the least possible score of 0 indicates no pain. Similarly visual analog scale (VAS) was used to record pain experienced by the child as per their parents. It is a validated, subjective measure for acute pain where zero is designated as "no pain" and 10 the "worst possible pain".

We did not include children receiving 1st and 3rd dose as they receive additional injectable polio vaccine which may interfere with the pain assessment. We also aimed at keeping the age of all subjects almost similar as the pain thresholds vary with age.

In our study about 56% of the subjects were males and about 44% were females. This was consistent with the Abbott[62] et al study from Canada where about 57% were males and 43% were females. Lindh[64] et al conducted a study in Sweden which also comprised of 58% males and 42% females.

In our study we also observed that there was no statistically significant difference in the pain scores with respect to gender i.e., mean MBPS scores in males and females were similar. This is in consistency with many other studies by Eland et al[72], Ipp et al[73], Megel et al[74], Cassidy et al[75] where this insignificance of gender has particularly been mentioned.

In this study we observed that the maximum pain was experienced at 1 minute post injection (6.32±1.46) irrespective of the intervention given. The MBPS pain score at 1 minute was ranging from 3 out of 10 to a maximum of 9 out of 10. Contrastingly, the MBPS scores observed at baseline (1.80±0.79) and after 5 minutes of injection (2.86±1.46) were quite low in comparison to the score at 1 minute.

A similar study by Cohen et al[63] also showed that total crying time post injection ranges from 0 to 90 seconds maximum in both the intervention and control group. Another study conducted by Maikler et al[2] showed that the total crying time lasts for about 35-70 seconds irrespective of the intervention. And therefore, the intervention we provide should primarily aim at reducing the duration of this initial period of distress.

In this study it was observed that children on whom topical local anaesthetic spray was applied pre-vaccination, they had lower pain scores in the opinion of both parents as well as the investigator. The MBPS score at 1 minute for LA spray

(5.11±1.1) which ranged from 3 to 7 and was significantly lower when compared to control (7.62±0.89) ranging from a score of 6 to 9. Similarly, the mean parental VAS score was lower in spray group (3.66±1.66) ranging from 0 to 8 when compared to control (5.82±2.56) which was ranging from 2 to 10.

Usage of refrigerant sprays could be dated back to the study by Maikler et al[2] in 1991 in which effect of cooling the skin of children undergoing immunization was studied. The study revealed that if skin refrigerant is used then less pain in terms of facial expression, latency to cry, duration of cry and body movements is experienced. Abbott et al[62] also supported the usage of refrigerant topical anaesthetic spray for pain management in short procedures like vaccination on the basis of four-point VAS scores where anaesthetic spray group had a lower mean score of 1.37±0.96 than the control group (2.03±0.93). Cohen et al[63] when comparing usage of vapocoolant spray and other interventions found that pain measures and cry duration was lesser in children on whom vapocoolant spray was used.

Our study shows that the use of EMLA cream was also beneficial in alleviating injection pain. The MBPS score at 1 minute for EMLA (6.22±1.14) which ranged from 4 to 8 was significantly lower when compared to control (7.62±0.89) ranging from 6 to 9. Similarly, the mean parental VAS score was lower in EMLA group (4.5±1.31) ranging from 2 to 7 when compared to control (5.82±2.56) ranging from 2 to 10.

This result was consistent with multiple studies done in past supporting the usage of EMLA cream. Taddio et al[57] in 1993 observed that pre-treatment of infants undergoing diphtheria-pertussis-tetanus (DPT) vaccination with EMLA was effective in reducing pain. This was expressed in terms of MBPS scores only and the median

difference of pre-vaccination and post-vaccination scores was significantly different between the control and intervention groups ($p<0.05$). In a study by Cohen et al[63] similar result was obtained. Lindh et al[64] also showed that the use of EMLA cream reduces pain and distress associated with vaccination in terms of MBPS scores.

When we compared the pain reducing ability of the two interventions in our study, it showed that local anaesthetic spray was more efficient than EMLA cream as per the MBPS where maximum score of 10 indicates worst pain experience and the least possible score of 0 indicates no pain. The mean MBPS score at 1 minute was least in the group using topical local anaesthetic spray with vapocoolant (5.11±1.1) followed by EMLA group (6.22±1.14) whereas control group (7.62±0.89) exhibited the maximum pain score values. This distribution of pain score at 1 minute between the interventions was statistically significant by Kruskal-Wallis (KW) test. Dunn's test for post-hoc analysis showed a significant difference in the distribution of pain scores at 1 minute between every pair of intervention A-B (p-value: <0.0001*), A-Control (p-value: <0.0001*) and B-Control (p-value: <0.0001*).

We also compared the parental opinion on pain experience of infants on the basis of visual analog scale (VAS) scores. Our study showed that usage of either EMLA cream or LA sprays had lower pain scores when compared to the control group. But among the two modalities, LA spray reduced pain in a better manner than EMLA cream in parents' opinion. The mean VAS score is least in group using topical local anaesthetic spray with vapocoolant (3.66±1.66) followed by EMLA group (4.5±1.31) whereas control group (5.82±2.56) exhibited the maximum pain score values as per parents. There is significant difference in the distribution of parental VAS between interventions by Kruskal-Wallis test. Dunn's test was used for post-hoc

analysis and it is observed that, there is significant difference in the distribution of parental VAS between every pair of intervention used. A-B (p-value: 0.0066*), A-Control (p-value: 0.0134*) and B-Control (p-value: <0.00001*).

Vapocoolant spray is better than EMLA cream even in terms of its cost effectiveness, convenience and fast acting nature. This was also stated in the study by Cohen et al[63] which compared the two modalities.

Each time EMLA cream is used, 1 hour waiting time is required and costs about Rs. 100 for each application including the cost of cream and the occlusive dressing. Whereas only 10 seconds are required for vapocoolant spray to act and costs about Rs. 15 for each application. Hence this proves the cost effectiveness and feasibility of using sprays from our study.

From this study we also observed that the parents were good at predicting pain in their children as the parental VAS scores correlated clinically to the MBPS scores and the order of pain scores obtained across each intervention groups is same, which is maximum in the control group and least in the group subjected to LA spray.

The strength of our study was the large sample size, maintenance of consistency of multiple factors during vaccination like age of the infant, site selection, length of needle, vaccine constituents and their properties, techniques of administering the injection so as to facilitate more accurate determination of pain lowering efficacy of local anaesthetic agents without any confounding factors.

But we still need to evaluate the use of LA spray in larger studies to prove that it can be used as an effective tool to minimise immunization pain in a cost effective and feasible manner.

The limitation of our study was the confinement of our study area only to the usage of local anaesthetics and its pain reducing ability. We did not consider multiple factors which could further help in alleviation of pain like usage of less painful formulations, positioning of child in mother's lap, techniques of distraction, use of oral sweetening agents like sucrose and breastfeeding during the procedure. Parental behaviours like non procedural talks, distraction, humor, empathy, criticism, reassurance, apologies which have an effect on coping mechanism of the child to pain were not evaluated.

A larger study in similar conditions with consideration of the above-mentioned factors will result in a better understanding of injection pain and development of more effective, less time consuming, cost-effective and feasible combined interventions to minimize vaccination related pain.

CONCLUSION

In the randomized controlled trial conducted in order to compare the efficacy of topical local anaesthetic spray with vapocoolant and EMLA cream to reduce injection pain during immunization, following conclusions could be drawn:

- The mean MBPS score at 1 minute was least in the group using topical local anaesthetic spray with vapocoolant (5.11±1.1) followed by EMLA group (6.22±1.14) whereas control group (7.62±0.89) exhibited the maximum pain score values.
- Similarly, mean VAS score is least in group using topical local anaesthetic spray with vapocoolant (3.66±1.66) followed by EMLA group (4.5±1.31) whereas control group (5.82±2.56) exhibited the maximum pain score values as per parents.
- Therefore, the local anaesthetic spray was more efficient than EMLA cream as per the MBPS scores as well as parental VAS scores.
- Vapocoolant spray is better than EMLA cream even in terms of its cost effectiveness, convenience and fast acting nature.
- The pain scores were not different with respect to gender i.e., mean MBPS scores in males and females were similar.
- The maximum pain was experienced at 1 minute post injection (6.32±1.46) irrespective of the intervention given when compared to MBPS scores observed at baseline (1.80±0.79) and after 5 minutes of injection (2.86±1.46). Therefore, the intervention we provide should primarily aim at reducing the duration of this initial period of distress.

SUMMARY

The study was an open label three-arm, randomized controlled trial which was done in KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi and Rukmini Nagar Urban Health Centre, Belagavi from September 2020 to September 2021. The study objective was to compare the pain reduction efficacy of topical local anesthetic spray with vapocoolant and EMLA cream during immunization. 228 children between the age of 9 and 11 weeks who were brought for immunization with 2nd dose of liquid pentavalent vaccine were enrolled for the study. They were randomized to three groups according to random number table and were subjected to the assigned intervention.

They were subjected to Modified Behavioral Pain Scale by the observer to assess the pain experienced by the infant before the injection, after 1 minute and after 5 minutes of injection. The 10-point MBPS assesses 3 behavioral components (facial expression, movements, and cry) as an indication of a child's experience of pain. Total score is the sum of scores in each parameter. Maximum score of 10 indicates worst pain experience and the least possible score of 0 indicates no pain. Parents also recorded their interpretation of pain experienced by their children using Visual Analog Scale which is a validated, subjective measure on a 10-point scale for acute pain where zero is designated as "no pain" and 10 the "worst possible pain".

It was observed that the post-injection MBPS pain scores were significantly low in the two intervention groups when compared to control. The mean MBPS score at 1 minute was least in the group using topical local anesthetic spray with vapocoolant (5.11±1.1) followed by EMLA group (6.22±1.14) whereas control group (7.62±0.89) exhibited the maximum pain score values. The same trend when also observed when parental VAS scores were compared. The mean VAS score is least in

group using topical local anesthetic spray with vapocoolant (3.66±1.66) followed by EMLA group (4.5±1.31) whereas control group (5.82±2.56) exhibited the maximum pain score values as per parents.

We also observed that the parents were good at predicting pain in their children as the parental VAS scores correlated clinically to the MBPS scores and the order of pain scores obtained across each intervention groups is same, which is maximum in the control group and least in the group subjected to LA spray. There was no difference in pain scores with respect to gender observed.

The study proves that LA spray is beneficial in reducing injection pain during vaccination of infants and can potentially be used in immunization clinics conveniently, easily and cost effectively.

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ANNEXURE-I

ETHICAL CLEARANCE LETTER

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed - to-be University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http\\www.jnmc.edu
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Ref: MDC/DOME/ 1420 **Date: 29/08/2020**

To,
REG NO.BM0119002
PG student in Paediatrics,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"A PROSPECTIVE RANDOMISED CONTROLLED TRIAL COMPARING THE EFFICACY OF TOPICAL LOCAL ANAESTHETIC SPRAY WITH VAPOCOOLANT VERSUS EMLA CREAM FOR PAIN ALLEVIATION IN INFANTS DURING VACCINATION",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi

150

ANNEXURE-II

INFORMED CONSENT

Title of the study:

A PROSPECTIVE RANDOMISED CONTROLLED TRIAL COMPARING THE EFFICACY OF TOPICAL LOCAL ANAESTHETIC SPRAY WITH VAPOCOOLANT VERSUS EMLA CREAM FOR PAIN ALLEVIATION IN INFANTS DURING VACCINATION

Respected Sir/Madam,

We would like to include your child in our study as he/she eligible for the same. During the study, you will be asked some questions in detail regarding your child.

Purpose of the study: To compare the pain reduction efficacy of using topical local anaesthetic spray with vapocoolant and EMLA cream during vaccination in children.

Risks and Benefits: The result of you taking part in this research will help healthcare providers in a better understanding regarding injection pain during the immunization process, and thus we will be able to provide improved patient care.

Alternatives: If you decide not to participate in this study, you will still be receiving the usual standard of care.

Privacy and confidentiality: Your privacy will be respected, and all information collected about you and your child during this study will be kept confidential. Your identity will remain undisclosed.

Relations with the Institutional policy: The J.N. Medical College will provide, within the limitations of the laws of the State of Karnataka, facilities and medical attention to patients who suffer injuries because of participating in this project.

Financial incentives: You shall not be receiving any payment or any financial incentives for participating in this study.

Authorization to publish results: The results of this study may be published for scientific purpose or presented to a scientific group. Your identity, however, will always be maintained confidential.

Voluntary participation: Your participation in this study is voluntary. Your decision whether to participate will neither affect the care of your child, nor your future relations with the doctor or the hospital. In the event, if the child suffers any physical injury or adverse event as the result of participation in this study, you may contact the investigator of the study.

In the event of an emergency, you should contact KLE'S Dr. Prabhakar Kore Hospital and MRC on Telephone No. 08312473777.

In case you need further information regarding your rights as a study participant, you may please contact DR. ROOPA M. BELLAD**,** chairman of the ethical committee, J N Medical College, Belagavi.

STATEMENT OF CONSENT

I, Mr./Ms/Mrs. _____ Parent/Guardian volunteer of _____ consent to include my child in this study. I have read the consent document, or it has been read to me in my vernacular language. I accept to participate in the study. All the information regarding this study is provided to me and I have understood the same. I have been given the opportunity to ask questions and obtain appropriate answers.

The signature or left thumbprint of Parent/Guardian:

Signature of the investigator:

Date:

ANNEXURE - III

PROFORMA

"A PROSPECTIVE RANDOMISED CONTROLLED TRIAL COMPARING THE EFFICACY OF TOPICAL LOCAL ANAESTHETIC SPRAY WITH VAPOCOOLANT VERSUS EMLA CREAM FOR PAIN ALLEVIATION IN INFANTS DURING VACCINATION"

Overall Serial No:

GROUP ALLOCATION: CONTROL / INTERVENTION A/B

Date:

Sociodemographic Particulars

Fathers' Name:

Profession:

Education:

Age:

Mother's Name:

Profession:

Education:

Age:

Permanent Residence:

Contact Telephone:

Baby's Name

Gender: Male/Female

Date of Birth:

Age:

Vaccination History

Previous Vaccination status: Unimmunized/Immunized

Injection given by:

Date & Time of Injection:

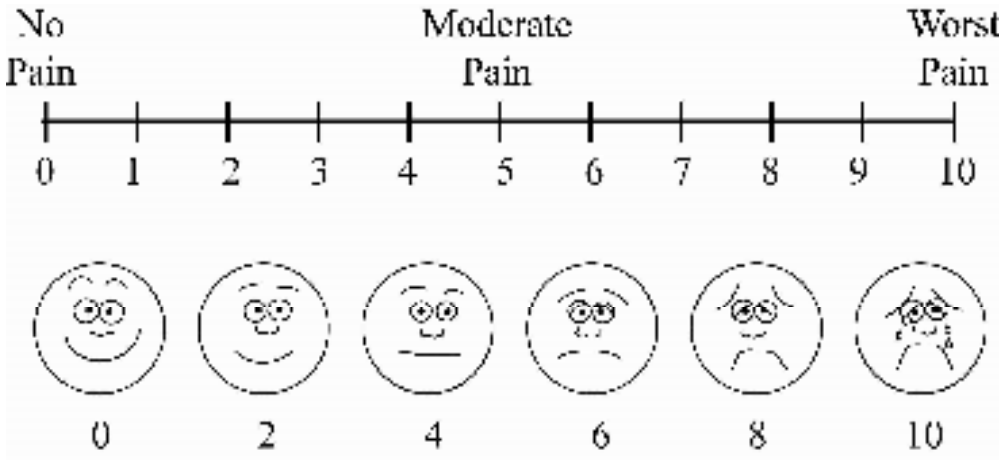
PAIN SCORES:

Modified Behavioral Pain Scale Score

	Pre-Injection	60s	5 minutes
MBPS:			

[redacted]

Parental VAS Score:



Visual Analogue Scale

(Signature of Investigator)

ANNEXURE - IV

RANDOMIZATION TABLE

Random numbers drawn from statistical software **R version 4.0.2.** Below table gives the randomization of subjects over group.

Group	Patients Number
Control	1, 3 , 7 , 9 , 16 , 27 , 28 , 31 , 32 , 39 , 41 , 42 , 43 , 48 , 52 , 55 , 58 , 59 , 64 , 72 , 75 , 79 , 80 , 82 , 84 , 86 , 88 , 89 , 94 , 97 , 99 , 101 , 106 ,111 , 112 , 117 , 119 , 120 , 123 , 124 , 126 , 129 , 132 , 133 ,134 , 136 , 139 , 143 , 146 , 149 , 150 , 151 , 157 , 160 , 161 ,163 , 166 , 168 , 176 , 177 , 178 , 187 , 193 , 194 , 201 , 203 ,204 , 205 , 207 , 208 , 213 , 216 , 220 , 222 , 224 , 225
A	6 , 10 , 12 , 19 , 20 , 21 , 23 , 24 , 25 , 26 , 30 , 33 , 38 , 40 , 46 , 47 , 49 , 54 , 56 , 60 , 61 , 63 , 65 , 70 , 73 , 77 , 81 , 85 , 92 , 100 , 102 , 103 , 104 ,107 , 108 , 110 , 116 , 121 , 122 , 127 , 128 , 135 , 144 , 145 ,148 , 152 , 153, 154 ,155 , 158 , 165 , 167 , 171 , 172 , 173 , 174 , 179 ,180 , 182 , , 184, 189 , 190 , 191 , 192 , 195 , 196 , 197 , 199 , 202 , 209 , 211 , 212 , 217 , 221 , 223 , 227
B	2 , 4 , 5 , 8 , 11 , 13 , 14 , 15 , 17 , 18 , 22 , 29 , 34 , 35 , 36 , 37 , 44 , 45 , 50 , 51 , 53 , 57 , 62 , 66 , 67 , 68 , 69 , 71 , 74 , 76 , 78 , 83 , 87 , 90 , 91 , 93 , 95 , 96 , 98 , 105 , 109 , 113 , 114 , 115 ,118 , 125 , 130 , 131 , 137 , 138 , 140 , 141 , 142 , 147 , 156 , 159 , 162 , 164 , 169 , 170 , 175 , 181 , 183 ,185 , 186 , 188 , 198 , 200 , 206 , 210 , 214 , 215 , 218 , 219 , 226 , 228

ANNEXURE V- MASTER CHART

Serial No.	Place	Intervention	Date of Birth (DD-MM-YYYY)	Date of Injection (DD-MM-YYYY)	Age in weeks	Gender	MBPS-0	MBPS-1 min	MBPS-5 min	Parental VAS
1	KLE	Control	04-07-2020	22-09-2020	11	FEMALE	3	7	4	5
2	KLE	B	21-07-2020	22-09-2020	9	FEMALE	3	5	2	4
3	KLE	Control	07-07-2020	22-09-2020	11	MALE	1	7	4	3
4	KLE	B	14-07-2020	22-09-2020	10	MALE	2	5	2	4
5	KLE	B	28-07-2020	29-09-2020	9	MALE	1	4	3	4
6	KLE	A	28-07-2020	29-09-2020	9	FEMALE	2	6	3	2
7	KLE	Control	28-07-2020	06-10-2020	10	FEMALE	1	8	4	10
8	KLE	B	21-07-2020	06-10-2020	11	FEMALE	1	4	3	6
9	KLE	Control	11-08-2020	13-10-2020	9	MALE	1	8	2	9
10	KLE	A	28-07-2020	13-10-2020	11	FEMALE	1	7	3	7
11	KLE	B	11-08-2020	13-10-2020	9	MALE	2	6	4	4
12	KLE	A	11-08-2020	20-10-2020	10	FEMALE	2	7	3	4
13	KLE	B	11-08-2020	20-10-2020	10	MALE	1	5	3	6
14	KLE	B	18-08-2020	20-10-2020	9	FEMALE	1	5	4	6
15	KLE	B	11-08-2020	27-10-2020	11	FEMALE	3	6	2	6
16	KLE	Control	11-08-2020	27-10-2020	11	MALE	2	7	2	9
17	KLE	B	25-08-2020	27-10-2020	9	MALE	2	4	2	2
18	KLE	B	25-08-2020	27-10-2020	9	MALE	1	5	2	2
19	KLE	A	25-08-2020	03-11-2020	10	MALE	3	8	2	6
20	KLE	A	25-08-2020	03-11-2020	10	MALE	2	7	2	4
21	KLE	A	25-08-2020	03-11-2020	10	MALE	3	7	2	5
22	KLE	B	18-08-2020	03-11-2020	11	FEMALE	2	6	4	2
23	KLE	A	08-09-2020	10-11-2020	9	MALE	1	6	2	5
24	KLE	A	01-09-2020	10-11-2020	10	MALE	1	6	3	7
25	KLE	A	25-08-2020	10-11-2020	11	MALE	2	5	3	6
26	KLE	A	25-08-2020	10-11-2020	11	MALE	2	6	3	3

27	KLE	Control	08-09-2020	10-11-2020	9	MALE	2	7	3	8
28	KLE	Control	08-09-2020	10-11-2020	9	MALE	2	8	2	10
29	KLE	B	01-09-2020	10-11-2020	10	MALE	2	5	3	2
30	KLE	A	08-09-2020	17-11-2020	10	MALE	3	5	4	4
31	KLE	Control	15-09-2020	17-11-2020	9	MALE	1	8	3	2
32	KLE	Control	15-09-2020	17-11-2020	9	FEMALE	2	9	2	8
33	KLE	A	15-09-2020	01-12-2020	11	MALE	3	5	3	5
34	KLE	B	15-09-2020	01-12-2020	11	MALE	3	5	3	2
35	KLE	B	22-09-2020	08-12-2020	11	FEMALE	3	6	3	0
36	KLE	B	06-10-2020	08-12-2020	9	FEMALE	3	6	2	4
37	KLE	B	06-10-2020	08-12-2020	9	FEMALE	3	4	2	2
38	KLE	A	06-10-2020	08-12-2020	9	MALE	3	4	4	2
39	RN	Control	01-10-2020	10-12-2020	10	MALE	1	9	2	5
40	RN	A	01-10-2020	10-12-2020	10	MALE	1	6	3	2
41	RN	Control	08-10-2020	10-12-2020	9	FEMALE	1	8	4	5
42	KLE	Control	29-09-2020	15-12-2020	11	MALE	1	8	4	2
43	KLE	Control	29-09-2020	15-12-2020	11	MALE	2	7	4	10
44	KLE	B	13-10-2020	15-12-2020	9	FEMALE	2	4	4	2
45	KLE	B	06-10-2020	15-12-2020	10	FEMALE	1	5	4	2
46	RN	A	01-10-2020	17-12-2020	11	MALE	1	6	4	4
47	RN	A	01-10-2020	17-12-2020	11	MALE	1	6	3	4
48	RN	Control	15-10-2020	17-12-2020	9	MALE	2	7	3	8
49	RN	A	15-10-2020	17-12-2020	9	FEMALE	2	8	4	4
50	RN	B	08-10-2020	17-12-2020	10	MALE	2	5	2	4
51	KLE	B	06-10-2020	22-12-2020	11	MALE	2	4	2	2
52	KLE	Control	06-10-2020	22-12-2020	11	MALE	2	6	3	4
53	KLE	B	20-10-2020	22-12-2020	9	FEMALE	1	4	3	4
54	RN	A	22-10-2020	24-12-2020	9	FEMALE	2	8	2	6
55	RN	Control	15-10-2020	24-12-2020	10	FEMALE	1	7	3	8
56	RN	A	08-10-2020	24-12-2020	11	FEMALE	2	7	2	5
57	RN	B	08-10-2020	24-12-2020	11	MALE	1	5	3	5

58	RN	Control	22-10-2020	24-12-2020	9	MALE	2	7	3	4
59	RN	Control	22-10-2020	24-12-2020	9	MALE	3	6	4	6
60	RN	A	15-10-2020	24-12-2020	10	FEMALE	1	7	2	5
61	RN	A	08-10-2020	24-12-2020	11	MALE	1	4	4	2
62	RN	B	08-10-2020	24-12-2020	11	FEMALE	1	5	3	4
63	RN	A	22-10-2020	24-12-2020	9	MALE	1	7	3	2
64	KLE	Control	27-10-2020	29-12-2020	9	FEMALE	3	7	4	10
65	KLE	A	20-10-2020	29-12-2020	10	MALE	3	6	3	3
66	RN	B	15-10-2020	31-12-2020	11	FEMALE	2	6	2	4
67	RN	B	15-10-2020	31-12-2020	11	FEMALE	2	6	2	4
68	RN	B	22-10-2020	31-12-2020	10	MALE	1	7	3	4
69	RN	B	29-10-2020	31-12-2020	9	MALE	1	6	4	4
70	RN	A	22-10-2020	31-12-2020	10	MALE	3	6	3	6
71	RN	B	15-10-2020	31-12-2020	11	MALE	3	5	2	6
72	KLE	Control	03-11-2020	05-01-2021	9	FEMALE	3	8	4	4
73	KLE	A	20-10-2020	05-01-2021	11	MALE	3	4	3	5
74	KLE	B	03-11-2020	05-01-2021	9	MALE	3	6	3	6
75	KLE	Control	20-10-2020	05-01-2021	11	MALE	3	8	2	2
76	KLE	B	03-11-2020	05-01-2021	9	MALE	3	5	3	2
77	KLE	A	27-10-2020	12-01-2021	11	MALE	1	4	2	5
78	KLE	B	03-11-2020	12-01-2021	10	FEMALE	1	6	2	4
79	KLE	Control	03-11-2020	12-01-2021	10	MALE	2	9	2	5
80	RN	Control	29-10-2020	14-01-2021	11	MALE	1	9	3	4
81	RN	A	12-11-2020	14-01-2021	9	MALE	1	7	2	4
82	RN	Control	12-11-2020	14-01-2021	9	MALE	3	8	3	6
83	KLE	B	03-11-2020	19-01-2021	11	FEMALE	1	6	4	2
84	KLE	Control	03-11-2020	19-01-2021	11	FEMALE	1	8	3	8
85	KLE	A	17-11-2020	19-01-2021	9	FEMALE	2	7	2	4
86	KLE	Control	17-11-2020	19-01-2021	9	FEMALE	1	8	2	8
87	KLE	B	10-11-2020	19-01-2021	10	MALE	2	3	3	4
88	KLE	Control	03-11-2020	19-01-2021	11	MALE	1	7	3	8

89	RN	Control	05-11-2020	21-01-2021	11	FEMALE	2	8	3	4
90	RN	B	12-11-2020	21-01-2021	10	FEMALE	2	4	3	2
91	RN	B	19-11-2020	21-01-2021	9	FEMALE	2	5	2	1
92	RN	A	12-11-2020	21-01-2021	10	FEMALE	2	4	4	4
93	RN	B	05-11-2020	21-01-2021	11	FEMALE	1	5	2	4
94	RN	Control	26-11-2020	28-01-2021	9	MALE	2	7	3	4
95	RN	B	12-11-2020	28-01-2021	11	MALE	1	3	3	4
96	RN	B	26-11-2020	28-01-2021	9	FEMALE	3	4	4	6
97	KLE	Control	17-11-2020	02-02-2021	11	MALE	2	7	2	8
98	KLE	B	01-12-2020	02-02-2021	9	MALE	3	4	4	2
99	KLE	Control	17-11-2020	02-02-2021	11	FEMALE	1	7	2	4
100	KLE	A	24-11-2020	02-02-2021	10	FEMALE	1	8	4	7
101	KLE	Control	24-11-2020	02-02-2021	10	MALE	1	8	2	4
102	KLE	A	17-11-2020	02-02-2021	11	MALE	1	8	3	6
103	KLE	A	01-12-2020	02-02-2021	9	FEMALE	1	7	4	5
104	KLE	A	01-12-2020	02-02-2021	9	MALE	2	6	3	4
105	KLE	B	17-11-2020	02-02-2021	11	MALE	3	6	3	6
106	KLE	Control	17-11-2020	02-02-2021	11	FEMALE	3	9	2	2
107	RN	A	03-12-2020	04-02-2021	9	MALE	2	7	4	7
108	RN	A	03-12-2020	04-02-2021	9	FEMALE	1	7	2	3
109	RN	B	26-11-2020	04-02-2021	10	FEMALE	2	7	2	5
110	RN	A	19-11-2020	04-02-2021	11	FEMALE	2	7	2	2
111	RN	Control	19-11-2020	04-02-2021	11	FEMALE	2	9	4	4
112	RN	Control	26-11-2020	04-02-2021	10	MALE	3	8	4	4
113	RN	B	03-12-2020	04-02-2021	9	FEMALE	1	6	2	4
114	KLE	B	01-12-2020	09-02-2021	10	FEMALE	1	6	2	2
115	KLE	B	24-11-2020	09-02-2021	11	FEMALE	2	5	3	2
116	RN	A	10-12-2020	11-02-2021	9	MALE	3	6	2	6
117	RN	Control	26-11-2020	11-02-2021	11	FEMALE	2	8	3	4
118	RN	B	10-12-2020	11-02-2021	9	FEMALE	1	6	3	8
119	KLE	Control	01-12-2020	16-02-2021	11	MALE	2	9	3	8

120	KLE	Control	15-12-2020	16-02-2021	9	FEMALE	1	9	3	6
121	KLE	A	01-12-2020	16-02-2021	11	MALE	1	5	2	7
122	KLE	A	08-12-2020	16-02-2021	10	MALE	1	5	2	4
123	KLE	Control	08-12-2020	16-02-2021	10	MALE	2	9	3	2
124	RN	Control	03-12-2020	18-02-2021	11	FEMALE	1	8	3	5
125	RN	B	17-12-2020	18-02-2021	9	MALE	3	7	4	4
126	RN	Control	17-12-2020	18-02-2021	9	MALE	2	8	4	3
127	RN	A	03-12-2020	18-02-2021	11	FEMALE	2	5	4	3
128	RN	A	03-12-2020	18-02-2021	11	MALE	1	7	3	5
129	KLE	Control	22-12-2020	23-02-2021	9	FEMALE	1	7	2	10
130	KLE	B	22-12-2020	23-02-2021	9	MALE	3	5	3	4
131	KLE	B	15-12-2020	23-02-2021	10	FEMALE	3	5	4	4
132	RN	Control	10-12-2020	25-02-2021	11	FEMALE	1	7	4	9
133	RN	Control	10-12-2020	25-02-2021	11	MALE	1	7	3	9
134	RN	Control	17-12-2020	25-02-2021	10	FEMALE	3	8	3	8
135	RN	A	24-12-2020	25-02-2021	9	MALE	1	7	3	4
136	RN	Control	17-12-2020	25-02-2021	10	FEMALE	3	9	4	10
137	KLE	B	15-12-2020	02-03-2021	11	FEMALE	1	7	4	6
138	KLE	B	29-12-2020	02-03-2021	9	MALE	1	6	2	4
139	KLE	Control	15-12-2020	02-03-2021	11	MALE	3	8	3	2
140	KLE	B	29-12-2020	02-03-2021	9	MALE	2	6	2	6
141	KLE	B	15-12-2020	02-03-2021	11	MALE	2	7	2	6
142	KLE	B	29-12-2020	02-03-2021	9	FEMALE	1	5	3	6
143	KLE	Control	15-12-2020	02-03-2021	11	FEMALE	1	8	3	8
144	KLE	A	22-12-2020	02-03-2021	10	MALE	2	5	3	3
145	RN	A	24-12-2020	04-03-2021	10	MALE	3	7	2	3
146	RN	Control	17-12-2020	04-03-2021	11	MALE	3	8	4	5
147	RN	B	31-12-2020	04-03-2021	9	FEMALE	1	5	3	2
148	RN	A	31-12-2020	04-03-2021	9	MALE	1	6	2	4
149	KLE	Control	22-12-2020	09-03-2021	11	FEMALE	3	7	4	5
150	KLE	Control	22-12-2020	09-03-2021	11	MALE	1	7	4	2

151	KLE	Control	05-01-2021	09-03-2021	9	MALE	2	6	4	10
152	KLE	A	05-01-2021	09-03-2021	9	FEMALE	1	6	4	5
153	KLE	A	29-12-2020	09-03-2021	10	MALE	1	5	4	6
154	KLE	A	29-12-2020	16-03-2021	11	MALE	2	6	2	6
155	KLE	A	29-12-2020	16-03-2021	11	FEMALE	2	5	2	5
156	KLE	B	05-01-2021	16-03-2021	10	MALE	1	5	3	2
157	KLE	Control	12-01-2021	16-03-2021	9	MALE	1	7	2	8
158	KLE	A	05-01-2021	16-03-2021	10	FEMALE	1	4	3	4
159	RN	B	31-12-2020	18-03-2021	11	MALE	2	3	2	2
160	RN	Control	14-01-2021	18-03-2021	9	FEMALE	3	8	2	4
161	RN	Control	31-12-2020	18-03-2021	11	MALE	1	9	2	8
162	KLE	B	19-01-2021	23-03-2021	9	FEMALE	2	3	2	2
163	KLE	Control	05-01-2021	23-03-2021	11	FEMALE	3	9	4	4
164	KLE	B	26-01-2021	30-03-2021	9	FEMALE	1	5	2	2
165	RN	A	14-01-2021	01-04-2021	11	MALE	1	4	3	5
166	RN	Control	21-01-2021	01-04-2021	10	FEMALE	3	8	2	6
167	RN	A	21-01-2021	01-04-2021	10	MALE	2	6	3	6
168	RN	Control	14-01-2021	01-04-2021	11	MALE	2	8	4	10
169	RN	B	28-01-2021	01-04-2021	9	FEMALE	2	5	2	0
170	RN	B	28-01-2021	01-04-2021	9	FEMALE	3	4	2	4
171	KLE	A	18-01-2021	05-04-2021	11	FEMALE	1	7	2	3
172	KLE	A	19-01-2021	06-04-2021	11	MALE	2	7	2	5
173	KLE	A	02-02-2021	06-04-2021	9	FEMALE	1	6	3	6
174	KLE	A	02-02-2021	06-04-2021	9	FEMALE	1	6	4	5
175	KLE	B	26-01-2021	06-04-2021	10	MALE	1	4	2	2
176	KLE	Control	19-01-2021	06-04-2021	11	MALE	2	7	2	4
177	RN	Control	21-01-2021	08-04-2021	11	FEMALE	1	9	3	2
178	RN	Control	28-01-2021	08-04-2021	10	MALE	1	7	3	5
179	RN	A	04-02-2021	08-04-2021	9	FEMALE	1	6	4	4
180	RN	A	28-01-2021	08-04-2021	10	MALE	3	6	2	3
181	KLE	B	02-02-2021	20-04-2021	11	MALE	1	3	2	2

182	KLE	A	16-02-2021	20-04-2021	9	MALE	3	7	2	5
183	KLE	B	02-02-2021	20-04-2021	11	MALE	2	6	2	2
184	KLE	A	16-02-2021	20-04-2021	9	MALE	2	8	3	6
185	KLE	B	02-02-2021	20-04-2021	11	FEMALE	1	7	3	4
186	KLE	B	16-02-2021	20-04-2021	9	FEMALE	2	3	4	2
187	KLE	Control	02-02-2021	20-04-2021	11	MALE	3	7	3	4
188	RN	B	11-02-2021	22-04-2021	10	MALE	3	7	3	4
189	KLE	A	16-02-2021	27-04-2021	10	FEMALE	2	7	3	5
190	KLE	A	09-02-2021	27-04-2021	11	MALE	2	8	3	4
191	KLE	A	23-02-2021	27-04-2021	9	MALE	1	8	2	4
192	KLE	A	23-02-2021	27-04-2021	9	MALE	1	7	2	3
193	KLE	Control	09-02-2021	27-04-2021	11	MALE	2	6	3	6
194	RN	Control	11-02-2021	29-04-2021	11	FEMALE	3	6	3	8
195	KLE	A	02-03-2021	04-05-2021	9	FEMALE	1	7	2	3
196	KLE	A	23-03-2021	25-05-2021	9	FEMALE	3	7	2	4
197	RN	A	18-03-2021	27-05-2021	10	MALE	1	6	2	5
198	RN	B	11-03-2021	27-05-2021	11	FEMALE	2	6	4	5
199	RN	A	11-03-2021	27-05-2021	11	MALE	2	6	2	4
200	KLE	B	23-03-2021	01-06-2021	10	FEMALE	3	4	3	4
201	KLE	Control	30-03-2021	01-06-2021	9	MALE	2	6	3	8
202	KLE	A	23-03-2021	01-06-2021	10	MALE	1	6	2	5
203	RN	Control	18-03-2021	03-06-2021	11	FEMALE	1	8	2	8
204	RN	Control	01-04-2021	03-06-2021	9	FEMALE	2	8	2	4
205	RN	Control	18-03-2021	03-06-2021	11	FEMALE	1	7	4	4
206	RN	B	08-04-2021	10-06-2021	9	MALE	1	4	4	4
207	RN	Control	25-03-2021	10-06-2021	11	MALE	2	7	3	8
208	RN	Control	08-04-2021	10-06-2021	9	FEMALE	1	7	3	4
209	KLE	A	30-03-2021	15-06-2021	11	MALE	3	7	3	4
210	KLE	B	06-04-2021	15-06-2021	10	MALE	1	5	2	4
211	KLE	A	06-04-2021	15-06-2021	10	FEMALE	1	7	4	5
212	RN	A	01-04-2021	17-06-2021	11	MALE	2	4	3	5

213	KLE	Control	20-04-2021	22-06-2021	9	MALE	1	8	3	4
214	KLE	B	20-04-2021	22-06-2021	9	FEMALE	2	6	2	4
215	RN	B	22-04-2021	24-06-2021	9	FEMALE	2	7	2	4
216	RN	Control	15-04-2021	24-06-2021	10	MALE	1	8	2	2
217	RN	A	08-04-2021	24-06-2021	11	MALE	1	5	4	6
218	KLE	B	27-04-2021	29-06-2021	9	MALE	3	5	4	6
219	RN	B	15-04-2021	01-07-2021	11	FEMALE	2	5	3	6
220	KLE	Control	04-05-2021	06-07-2021	9	MALE	1	6	2	4
221	KLE	A	20-04-2021	06-07-2021	11	MALE	3	6	3	5
222	KLE	Control	04-05-2021	06-07-2021	9	FEMALE	3	6	2	4
223	KLE	A	27-04-2021	13-07-2021	11	FEMALE	2	7	4	4
224	KLE	Control	04-05-2021	13-07-2021	10	FEMALE	1	8	2	4
225	KLE	Control	04-05-2021	13-07-2021	10	FEMALE	1	7	3	8
226	KLE	B	27-04-2021	13-07-2021	11	FEMALE	1	4	2	2
227	KLE	A	11-05-2021	13-07-2021	9	MALE	2	7	2	4
228	RN	B	13-05-2021	15-07-2021	9	MALE	1	4	4	4