Original Research Article

Effectiveness and Safety of Ketamine and Fentanyl as an Adjuvant to Bupivacaine for Caudal Block in Pediatric Subumbilical Surgeries

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Abstract

Background: To compare Effectiveness of Ketamine and Fentanyl as an adjuvant to Bupivacaine for postoperative analgesia in children undergoing sub umbilical surgeries under caudal epidural block. Secondary aim: To study the side effects if any **Materials and methods:** A total of 90 children aged between 2-6 years ASA I and ASA II undergoing sub umbilical surgeries were included in this prospective, randomized, double blinded study. Three groups of 30 each were assigned to receive caudal block with Bupivacaine 0.25% 1ml/kg along with either 0.9%normal saline (GROUP I), 0.5ug/kg Fentanyl (GROUP II) or 0.5mg/kg preservative free Ketamine (GROUP III). Postoperative pain was assessed using the FLACC score. Postop duration of analgesia and requirement of rescue analgesics for 24 hours were monitored along with hemodynamics. **Results**: The data was considered significant if p values equal to or less than 0.05 and highly significant if p value <0.001. FLACC score was significantly lower in GROUP III. Duration of analgesia was prolonged in GROUP III (p value <0.05) compared to GROUP I and GROUP II. **Conclusion**: Our study showed that addition of preservative free Ketamine as an adjuvant to Bupivacaine increases the duration of analgesia postoperatively. We recommend that it is always better to use Ketamine as an adjuvant, as it gives better analgesia than Fentanyl without any side effects.

Keywords- Bupivacaine; Caudal; Fentanyl; FLACC score; Postoperative analgesia; Preservative free Ketamine

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INTRODUCTION

Caudal epidural anaesthesia is most commonly practiced regional technique in children for sub umbilical surgeries. It also reduces stress response to surgery and decreases the requirement of general anaesthetic drugs. The main disadvantage of Caudal anaesthesia is short duration of action after single injection of local anaesthetic solution. The use of caudal catheter to administer repeated doses of infusion of local anaesthetic is usually not practiced due to concerns about proximity to anorectal area giving rise to infection and toxicity risks. In recent years, addition of adjuvants to local anaesthetics has resulted in prolonging duration of block, improved pain control, parental separation and faster recovery. So, various adjuncts have been used previously to prolong the duration of caudal analgesia.

Most commonly used drugs as an adjuvants are Clonidine, Ketamine, Opioids, Dexmedetomidine, Dexamethasone, $MgSO_4$, Neostigmine. Recently preservative free Ketamine (absence of Benzethonium chloride and Chlorambutanol which possibly causes neurotoxicity) has proven its efficacy as an adjuvant to local anaesthetics in Caudal block for improving the duration and quality of postoperative analgesia and reduce the need for additional analgesic requirement without significant hemodynamic or respiratory effects. Caudal administration of an adjuvant to

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enhance the effect of local anaesthetic is based on concept that it will increase the concentration of the drug in the cerebrospinal fluid, producing a more localized effect at the spinal cord level.

Our study aims at to compare effectiveness of Ketamine and Fentanyl as an adjuvant to Bupivacaine for postoperative analgesia in children undergoing sub umbilical surgeries under caudal epidural block. Also, to find need of total rescue analgesics over 24 hours, perioperative haemodynamic safety and complications (like nausea, vomiting, pruritus, respiratory depression, urinary retention etc.)

MATERIALS AND METHODS

This is Hospital based Prospective, randomized, double blinded comparative study was conducted in Surgery operation theatre and its respective wards in our institute which is a tertiary care hospital for duration of one year. After obtaining Institutional Ethical committee approval, a total 90 children were randomly allotted to Three equal groups. Each group contain 30 children of either sex of age group 1-6 years of American Society of Anaesthesiologist I and II undergoing sub umbilical surgeries (for examples Hernioplasty and herniotomy, Orchidopexy, Hydrocele, Circumcision, Urethroplasty, Hypospadias repair) who required Caudal block. A minimum of 88 patients were required in each group to achieve a significance level of 95% and power of 80%with type I (α) error of 0.05. Hence, we included 30 patients in each group to consider any dropouts. Informed, written, valid consent was taken from the parents who's children are posted for sub umbilical surgeries before inclusion into this study in their language. Patient and parent refusal, children having history of allergy to study drug, infection present at site of caudal block, coexisting coagulopathy, any neurological condition or failed block, caudal vertebral anomalies were excluded from this study.

A day before surgery along with pre anaesthetic evaluation, the procedure of block along with possible complications was explained to parents. Preoperative baseline investigations were done. Parents were instructed to keep the children nil orally upto 6 hours before surgery and intravenous maintenance fluid was started at 4ml/kg/hr. In preoperative after securing peripheral intravenous access patients were premedicated with inj Glycopyrolate 0.004mg/kg IV and inj Midazolam 0.03mg/kg just before surgery.

In Operation Theatre after ensuring resuscitation equipment ASA standard monitors ECG, NIBP, pulse oximeter and calculated fluid were attached and baseline parameters were recorded. Inhalational induction was done with oxygen, nitrous oxide and sevoflurane delivered through Jackson Rees modification of Ayre's T-piece and face mask, with standard monitoring. Appropriate size LMA was inserted and anaesthesia was maintained with 30% oxygen, 70% nitrous oxide and Svoflurane 1.5%with fresh gas flow 4 liters/min.

The studied drug was loaded in insulin syringe for precise dose administration according to weight. Studied drug is prepared by anaesthesiologist who was not included in study. After induction patient was placed in left lateral decubitus position and a single shot caudal block was performed with aseptic precautions, using 23 G hypodermic needle by an anaesthesiologist who was blinded to the caudally administered drug. Patients were randomised, Group BC received 0.25% Bupivacaine 1ml/kg in 0.9% normal saline. Group BF received 0.25% Bupivacaine 1ml/kg and 0.5ug/kg Fentanyl. Group BK received 0.25% Bupivacaine and 0.5mg/kg preservative free Ketamine.

After confirming correct placement of needle and negative aspiration of blood and CSF, the respective drug solution was injected. Surgery was allowed to start after 10min of caudal block. Depth of anaesthesia was maintained with 2% sevoflurane and caudal block. Heart rate (HR), Mean arterial pressure (MAP), SPO2, Respiratory rate (RR), were recorded preoperative before induction, after induction and then every 5 min after Caudal block upto 30 min. Intraop and postop decrease in HR and MAP by more than 30% of its baseline was decided to treat with rapid infusion of fluids and with 0.01mg/kg inj Atropine IV if required. At the beginning of skin closure, sevoflurane and nitrous oxide were disconnected. At the end of surgery LMA was removed and patient was shifted to recovery room, breathing room air.

Postoperatively along with HR, MAP, SPO2, RR patients were assessed for postoperative pain by FLACC score and postoperative sedation by Ramsay sedation score. Patients were also monitored for nausea, vomiting, pruritus and respiratory depression, nystagmus, motor weakness, urinary retention in 24 hours. FLACC score has five variables which include (Face, Leg, Activities, Cry, Consolability). Each variable having 0,1,2 score to give a cumulative score of 0-10. If this score was 4 or more it was considered that the analgesic action of caudally administered drug had terminated and patient had received fixed dose of rescue analgesics as IV inj Paracetamol 15mg/kg. Need of total no. of doses of rescue analgesics over 24 hrs was recorded in all three study groups. Duration of postop analgesia is defined as time between administration of studied drugs and first need for rescue analgesia. Postop monitoring was done at 2,4,6,8,10,12,24 hrs.

Intraop increase in HR and MAP by more than 15% of baseline values was decided to treat with inj Fentanyl 2ug/kg. The block was considered as failed if intraoperative intravenous analgesics were required due to inadequate analgesia and was excluded from study.

Sedation was assessed by 4 point Ramsay sedation score- (0) Eyes open spontaneously, (1)Eyes open to verbal stimulation , (2)Eyes open to physical stimulation , (3)Unarousable

RESULTS

Data analysis was done by appropriate statistical method with EPI INFO VERSION 7 software. Results were expressed as means ± standard deviation of the means (SD) or number (%). Categorical data was analysed by ANOVA test for comparison between three groups.

The data was considered significant if p value ≤ **0.05** and highly significant if p value ≤**0.001**.

The patients in all three groups were comparable with respect to age, body weight, duration of surgery, type of surgery. It was found that there was no statistical difference between the three groups with respect to these parameters.

There were no significant differences in Heart Rate, MAP, RR, SPO2 comparing in all three groups. No significant changes were observed in sedation score in all three groups. None of the patients required additional analgesics in intraoperative period. None of patient had postop nausea, vomiting, itching, shivering amongst all study population.

All three groups were comparable for FLACC score at 6th hour, Duration of analgesia in hours and total no. of rescue analgesics in 24 hrs. Group BK had significantly lower pain score (2.93±1.26) than Group BF (4.1±0.77) and Group BC (4.93±0.91) which showed highly significant difference(p=0.001).

Group BK had mean duration of postop analgesia of 13.3± 5.19 hours, Group BF had 9.16±2.88 and Group BC had 6.03±2.02. Duration of postop analgesia was significantly higher in Group BK (p=0.001)

The mean number of doses of rescue analgesia that patients received in 24 hours in Group BK, Group BF and Group BC were 1.1 0.80, 1.86 0.79 and 2.43 0.86 respectively showing highly significant difference(p=0.001).

Table 1: DEMOGRAPHIC PARAMETERES

	Group B+C mean±SD	Group B+F mean±SD	Group B+K mean±SD	P value
Age(2-6years)	3.76 ±1.42	3.8± 1.42	3.76± 1.47	0.99
Weight	14 ±4.68	13.9± 4.97	13.6 ±4.85	0.94
Sex(M/F)	25/5	26/4	25/5	
ASA(I/II)	24/6	25/5	24/6	
Duration of surgery(min)	41.8±16.9	40± 15.91	40±15.9	0.88

Table 2: Hemodynamic parameters

Mean HR	Group B+C Mean±SD	Group B+F Mean±SD	Group B+K Mean±SD	P value
Baseline HR	103±14.6	100± 13.3	101±13.8	0.71
Preop HR	107±13.2	103± 13.2	105±12.9	0.50
Intraop HR	101±13.5	95± 10.9	97±11.1	0.22
Postop HR	99±13.3	94± 11.0	92±10.9	0.17

Table 3

Mean MAP	Group B+C Mean±SD	Group B+F Mean±SD	Group B+K Mean±SD	p value
Baseline MAP	85.3±6.80	84.4± 7.42	84.5±6.87	0.86
Preop MAP	85.4±6.36	85.6± 7.55	85.1±6.85	0.96
Intraop MAP	83.2±6.86	81.7± 7.71	81.2±7.46	0.54
Postop MAP	82.4±6.82	80.4± 7.67	78.7±7.72	0.16

Table 4: POSTOP PAIN CHARACTERISTICS

	Group B+C Mean±SD	Group B+F Mean±SD	Group B+K Mean±SD	P value
FLACC pain score at 6th hr	4.93±0.91	4.1± 0.77	2.93±1.26	**0.001**(significant)
Duration of analgesia(hrs)	6.03±2.02	9.16± 2.88	13.3±5.19	**0.001**(significant)
Total no. of Rescue analgesic dose in 24 hrs	2.43±0.86	1.86± 0.79	1.1±0.80	**0.001**(significant)

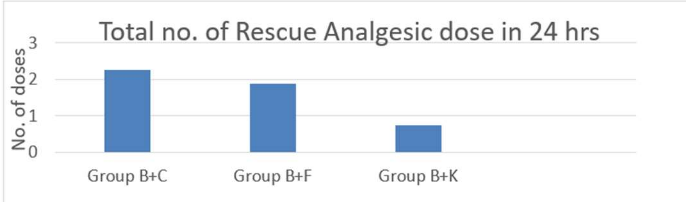

Figure 1

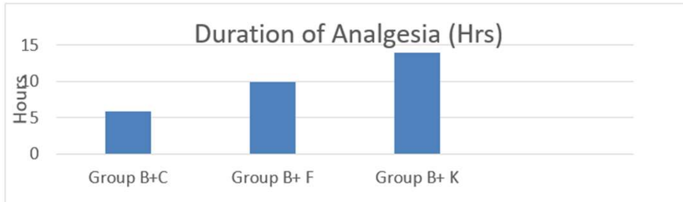

Figure 2

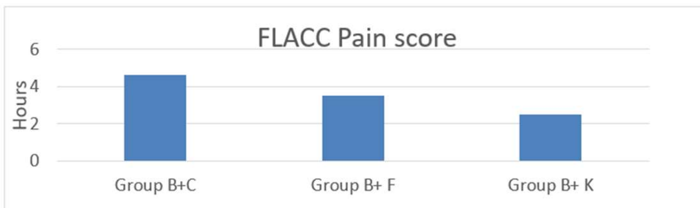

Figure 3

DISCUSSION

Postoperative pain management is an integral part of practice of paediatric anaesthesiologist as it is a very complex phenomenon and is very difficult to differentiate restlessness or crying due to pain from hunger or fear in children. The limitation of single shot caudal block is its finite and short duration, which reduces its utility as postoperative analgesics. Even long-acting analgesic drug such as Bupivacaine provides only 4-6h of analgesia.

Bupivacaine is most common local anaesthetic used in blocks. It is an Amino amide derivative. It binds to intracellular portion of voltage gated sodium channels and blocks sodium influx into nerve cells, preventing depolarisation.

Ketamine is a derivative of phencyclidine group, has a chemical structure similar to that of Bupivacaine and therefore has local anaesthetic effects. It uncompetitively blocks NMDA receptor- type of Glutamate receptor, opioid u receptor agonist and voltage sensitive Sodium channel interaction. Ketamine functionally dissociates sensory impulses from Limbic cortex. The antinociceptive action of Ketamine is also associated with u opioid receptors and may involve activation of descending inhibitory monoaminergic pain pathway.

Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist, structurally related to meperidine. It has more rapid onset and short duration of action. Opioid induced side effects are nausea, vomiting, respiratory depression, pruritus, urinary retention etc.

Semple et al (1996) conducted a study in three groups of children undergoing sub umbilical surgeries which compared the 0.25mg/kg, 0.5mg/kg and 1mg/kg dose of caudal ketamine with 1ml/kg of 0.25% Bupivacaine. They concluded that the optimum dose of ketamine for caudal epidural blockade is 0.5mg/kg. Hence to avoid behavioural side effects caused by higher dose of Ketamine we used 0.5mg/kg dose.

Naguib et al (1991) compared the analgesic effects of 0.25% Bupivacaine 1ml/kg with and without Ketamine in dose of 0.5mg/kg in children undergoing inguinal herniotomy. It is found that there was no significant difference in the quality of analgesia between the groups, only 7% of patients in Ketamine + Bupivacaine group required analgesia in the first 24 hours after surgery compared with 20% and 50% respectively in Ketamine only and Bupivacaine only groups.

Similarly *Cook et al* (1995) conducted a study in three groups of children undergoing Orchidopexy. It is found that addition of Ketamine 0.5mg/kg to Bupivacaine 0.25% (1ml/kg) provided a longer median duration of postoperative analgesia (12.5 h) than either clonidine 2ug/kg (5.8 h) or epinephrine 5ug/ml (3.2 h).

Desai Dj et al (2008) compared two different doses of Fentanyl in two groups in children undergoing lower abdominal or lower limb surgeries. They found that both

the dosed 1ug/kg and 0.5ug/kg of Fentanyl with Bupivacaine 0.25% when administered caudally provided satisfactory surgical anaesthesia without any haemodynamic disturbances with prolonged duration of analgesia with Fentanyl 1ug/kg as compared to 0.5ug/kg without any major postoperative complications. However, in few studies it is found that Hypotension and Bradycardia were more with 1ug/kg Fentanyl. In our study we chose 0.5ug/kg Fentanyl dose and did not find any incidence of significant hypotension, bradycardia, respiratory depression in Fentanyl group.
Ahuja S et al (2015) compared efficacy of Fentanyl and Ketamine on postoperative pain and neuroendocrine stress response in children undergoing infraumbilical and perineal surgeries. They conclude that Ketamine at a dose of 0.5mg/kg when used as an adjuvant to Bupivacaine is better than Fentanyl 1ug/kg in terms of analgesia as well as blunting of stress response.
Swami SJ et al (2015) conclude that addition of Fentanyl 1ug/kg or Ketamine 0.5mg/kg to caudal Bupivacaine prolongs postoperative analgesia in children undergoing genitourinary and lower limb surgery. Caudal Fentanyl with Bupivacaine does not increase the incidence of postoperative respiratory depression, however postop pain relief is significantly prolonged with Ketamine as compared to Fentanyl, which was similar to what we observed in our study.
Locatelli et al (2005) and *Breschan et al* (2005) concluded from their study that Bupivacaine and Levobupivacaine are equally potent and had longer analgesic effect. Hence, we decided to use 0.25% Bupivacaine for our study.
Campbell FA et al (1992) compared the analgesic efficacy and safety of a single caudal injection of Bupivacaine Fentanyl combination in children undergoing urological surgeries in a prospective, controlled, triple blinded study. They did not find any opioid induced complications which is in favour of our study.
Dalens and Hasnaoui recommend caudal volumes between 0.7 and 1.0ml to achieve an adequate level of analgesia for inguinal surgery, as higher concentration of drug gives better analgesia which is consistent to our study in which we used 1ml/kg volume of Bupivacaine.
We chose FLACC score over other scores to evaluate postoperative pain as it is easy to use, validated and avoid subjective evaluation done by parents. In our study we monitored patient for 24 hours which is in contrast to few studies in which they used 6 hours of postop pain monitoring and rest assessment was done by parents.
Intraop and postop stability of Haemodynamic parameters, absence of opioid free side effects and decreased requirement of analgesics goes in favour of using Ketamine Bupivacaine combination for paediatric caudal block.
Our study had certain limitations. The patient profile (2-6 years) of our study makes it difficult to distinguish between sedation and analgesia as a pain free child is comfortable and asleep.
We recommend that addition of Preservative free Ketamine to Bupivacaine for caudal epidural analgesia because of its multiple advantages like no neurotoxicity, increased analgesic potency over commercially available racemic Ketamine. Also it is always better to use Ketamine over Fentanyl for Opioid free anaesthesia and analgesia, better control of intraoperative and postoperative hemodynamic, significantly longer duration of postoperative analgesia, almost no incidence of opioid side effects.

CONCLUSION

Addition of Fentanyl 0.5ug/kg or Ketamine 0.5mg/kg to caudal Bupivacaine prolongs postoperative analgesia in children undergoing sub umbilical surgeries. Single shot caudal injection of Ketamine added to Bupivacaine, offers an advantage of prolonged postoperative pain relief over Bupivacaine with Fentanyl. We recommend to use Preservative free Ketamine as an adjuvant to local anaesthetic agent in caudal block as it gives optimum analgesia without any side effects.

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