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A Prospective Randomized Double Blind Study for Comparative Evaluation of Bupivacaine with Two Different Doses of Clonidine for Pediatric Caudal Analgesia in Infra Umbilical Surgeries

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Abstract

Introduction: We designed a double blind randomized controlled trial to comparatively evaluate the efficacy of bupivacaine with two different doses of clonidine for pediatric caudal analgesia in infra umbilical surgeries. *Methodology:* 90 children, 2-10 years of age, weight < 20 kg of either sex, belonging to ASA grade I and scheduled for infra umbilical surgeries were taken up for the study. Patients were divided randomly into three groups of 30 each using the computer generated technique- Group 1- 0.75 ml/ kg of 0.25% bupivacaine and 1µg/ kg of clonidine; Group 2 - 0.75 ml/ kg of 0.25% bupivacaine and 2µg/ kg of clonidine. Group 3: 0.75 ml/ kg of 0.25% bupivacaine. 0.75 ml/ kg of the study drug solution was injected after administration of anaesthesia. Post operative monitoring for heart rate, blood pressure, respiratory rate, SpO_2; Post operative analgesia- using Modified Objective Pain Score. Post operative sedation score using the Four Point Sedation Score was done at the interval of 0, ½, 1, 2,4,8,12,24 hours. *Results:* Efficacy of Post operative analgesia assessed by MOPS score was found to be better in group 2 followed by group 1 and least in group 3. Also, post operative sedation score was highest in Group 2 as compared to group 1 & 3. *Conclusion:* We recommend a dose of 1µg/kg clonidine as an adjuvant to 0.25% bupivacaine (0.75ml/kg) for infra-umbilical surgeries to significantly prolong post-operative analgesia without causing significant sedation. Increasing the dose of clonidine to 2µg/kg didn't significantly prolong postoperative analgesia but did produce significant sedation, which might interfere with discharge criteria for day care surgery.

Keywords: Pediatric Caudal Analgesia; Infra Umbilical Surgeries; Clonidine; Bupivacaine.

Introduction & Background

Caudal epidural analgesia is a reliable and safe technique that can be used with general anaesthesia for infra umbilical and post operative analgesia in patients undergoing lower abdominal, urological and lower limb surgeries [1,2].

The major limitation of single injection technique is the relatively short duration of post operative analgesia (4-6 hr) that accompanies the use of even long acting local anesthetic agent like bupivacaine [2,3]. The most frequently used method to further prolong post operative analgesia following caudal block is to add different adjuncts to local anesthetic solutions each of which has its limitations including significant side effects like respiratory depression, nausea, vomiting, urinary retention, pruritis and neurotoxicity [1,2,3].

Clonidine, an α_2 adrenergic agonist, produces analgesia without significant respiratory depression after systemic, epidural or intrathecal administration. Although epidural clonidine has been associated with reduction in heart rate and arterial pressure in adults, these hemodynamic side effects appear to be less pronounced in children [2,10]. The analgesic action of intrathecal or epidural clonidine results from direct stimulation of pre and postsynaptic α_2 adrenergic receptors in the dorsal horn grey matter of the spinal cord, inhibiting the release of nociceptive neurotransmitters [2,6].

Many studies have shown that addition of clonidine to epidurally administered bupivacaine prolongs the duration of post operative analgesia in children. However doses of clonidine used by different authors are variable

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[1,2,3].

W. Klimscha et al (1998) studied the efficacy and safety of clonidine and bupivacaine combination in caudal blockade for pediatric hernia repair in 58 patients. These authors reported significantly longer duration of analgesia with 0.25% bupivacaine 0.75 ml/kg combined either with 1 µg/kg clonidine (median 360 minutes) or clonidine 2 µg/kg (median 360 minutes) as compared to bupivacaine with or without epinephrine 1: 200000 (300-340 minutes respectively) in a 6 hour observation period. They also observed that clonidine group in their study required significantly lesser supplementary analgesia within the first 24 hrs [1].

In 1993, a study by J.J.Lee et al in 40 children aged 1 to 10 years undergoing elective orthopedic surgeries assessed the efficacy of combining clonidine with bupivacaine for caudal analgesia. Their study revealed that addition of clonidine 2 µg/kg to 0.25% bupivacaine 1 ml/kg significantly prolonged the duration of caudal analgesia compared with that provided by bupivacaine alone (9.8 hrs. and 5.2hrs. respectively) , without an increase in the incidence of side effects in children undergoing orthopedic surgeries. However, the duration of analgesia was considerably shorter than that reported by Jamali and colleagues (mean of 987 mins) for the clonidine group, despite the administration of twice the amount of clonidine in their study [9].

Samir Jamali et al (1994) assessed the efficacy of clonidine with bupivacaine compared to epinephrine and bupivacaine for caudal analgesia in 45 pediatric patients of ages 1 to 7 years, scheduled for sub-umbilical surgeries. Their study demonstrated that addition of 1µg/ kg of clonidine to a caudal block with 0.25 % bupivacaine 1 ml/kg as compared with bupivacaine with and without epinephrine, increases the duration of post operative analgesia in pediatric patients, the mean duration of analgesia being 16.8 hrs, 4.7 hrs and 7.5 hrs for clonidine, epinephrine and plain bupivacaine groups respectively [7].

DA. H de Beer and M. L. Thomas (2003) in the review article on caudal additives in children had observed that caudal analgesia remained the most popular and commonly used regional block in pediatric Anaesthesia. They have stated that bupivacaine is the most widely used local anesthetic used for this technique and provides post operative analgesia lasting 4 to 8 hours. They have also stated that extended duration of analgesia that can be achieved by using caudal additives is significant but whether the perceived benefits justified the potential risks and which is the ideal agent needs further study. Clonidine as an additive to caudal bupivacaine, has been shown to improve the efficacy and duration of post-operative analgesia in children by several authors, however the duration of analgesia varies widely in these studies [2].

James Eisenaah et al (1993) studied the hemodynamic and analgesic action of epidurally administered clonidine (lumbar epidural) in nine adult volunteers. They monitored the BP/HR, finger and toe blood flow and response to cold pain testing while sampling CSF & arterial plasma for clonidine analysis. They correlated the effects to plasma and CSF clonidine concentration. They concluded that in comparison to potent opioid Alfentanyl administered as IV infusion to other volunteers, epidural clonidine produces a similar degree of analgesia but less respiratory depression [5].

A.M.EL.Hennaway et al (2009) studied the efficacy of addition of clonidine or dexmedetomidine to bupivacaine for prolonging paediatric caudal analgesia in 60 children. They concluded that addition of dexmedetomidine 2 µg/kg or clonidine 2 µg/kg to caudal bupivaciane 0.25 % of 1 ml/kg significantly promotes analgesia time after anesthetic recovery in children aged 6 months to 6 years, undergoing lower abdominal surgeries without increasing the side effects. Moreover, dexmedetomidine did not offer significant advantages over clonidnine with regard to the analgesia duration [8].

Archana Kaul et al (2009) evaluated the analgesic efficacy, hemodynamic and respiratory safety of clonidine 2 µg/kg with 0.25% bupivacaine 0.75 ml/kg for caudal block in 40 children undergoing inguinal hernia repair. They concluded that addition of clonidine in caudal block prolongs post operative pain relief in children (10.25± 3 hrs) and is a safe alternative to bupivacaine alone in pediatric day care surgeries [10].

We, therefore, designed a double blind randomized controlled trial to comparatively evaluate the efficacy of bupivacaine with two different doses of clonidine for pediatric caudal analgesia in infra umbilical surgeries.

Aims and Objectives

1. To evaluate the efficacy of two different doses of clonidine as an adjuvant to caudal bupivacaine for providing postoperative analgesia in pediatric patients undergoing infra umbilical surgeries.
2. To compare the above two groups with bupivacaine alone for caudal analgesia in

pediatric patients undergoing infra umbilical surgeries.

Materials and Methods

After obtaining approval of the hospital ethics committee, this randomized controlled double blind study was conducted in the department of Anaesthesia and Intensive care, Safdarjung hospital & VMMC, New Delhi.

Patient Selection

90 children, 2-10 years of age, weight < 20 kg of either sex, belonging to ASA grade I and scheduled for infra umbilical surgeries were taken up for the study. Patients were divided randomly into three groups of 30 each using the computer generated technique.

Group 1: 0.75 ml/ kg of 0.25% bupivacaine and 1µg/ kg of clonidine.

Group 2: 0.75 ml/ kg of 0.25% bupivacaine and 2µg/ kg of clonidine

Group 3: 0.75 ml/ kg of 0.25% bupivacaine.

Exclusion Criteria

- History of allergic reaction to local anesthetics.
- Bleeding diathesis.
- Pre existing neurological and spinal disease.
- Local and systemic infections.
- Parental refusal.

Pre Operative Preparation

A detailed pre anaesthetic check up was done for all patients as per standard protocol. Parents of children were explained about the procedure and nature of the study and informed consent was obtained from them explaining all the risk and benefits. All children were premedicated with Syrup Trichlofos 70 mg/kg two hours before procedure.

Anesthetic Technique and Intraoperative Management

Induction

All patients were administered general Anaesthesia with inhalational induction using O_2/ N_2O (50:50) and Sevoflurane 6-8 % using Jackson-Rees modification of Ayre's T piece and face mask. Intravenous line was secured immediately after induction. Fentanyl in a dose of 2 µg/ kg was administered intravenously. An appropriate sized Proseal LMA was inserted and proper positioning confirmed by auscultation and Capnography.

Caudal Block

The child was then turned to the left lateral position and caudal block was administered under aseptic precautions using a 23G hypodermic needle of short bevel and a total volume of 0.75 ml/kg of the study drug solution was injected after ensuring proper placement of the needle at 45° to the skin by repeated negative aspiration for CSF and blood.

Maintenance

Anaesthesia was maintained with O_2/N_2O (33:67%) and sevoflurane 2-4% with manual assistance and a fresh gas flow of 2-3 times the minute ventilation. Intravenous fluid given intra operatively was ringer lactate in standard doses. Any decrease in mean arterial pressure or heart rate more than 30% of baseline value was defined as severe hypotension or bradycardia respectively and treated with rapid infusion of intravenous fluid with injection ephedrine and atropine.

Rescue analgesia with syrup paracetamol (20 mg/ kg) or injection paracetamol (10 mg/kg IM) if patient not allowed orally, was given only on demand or if the pain score is more than equal to 4.The total dose of rescue analgesia administered in 24 hrs was noted.

Intraoperative Monitoring

Intraoperative monitoring included the following parameters which were recorded before operation and every five minutes until the end of surgery.

1. Heart rate
2. Blood Pressure
3. Respiratory Rate
4. SpO_2
5. Et CO_2
6. ECG

Reversal

At the completion of surgery, all anaesthetic agents were discontinued and LMA removed after patient was awake. Patient was then transferred to recovery room.

Post Operative Monitoring

Patient was monitored for two hours in the recovery room and subsequently in the pediatric ward for up to 24 hours after surgery. Following parameters were monitored at the interval of 0,1/2,1, 2,4,8,12,24 hours.

1. Vital parameters- heart rate, blood pressure, respiratory rate, SpO_2.
2. Post operative analgesia- Pain scoring was done using Modified Objective Pain Score (MOPS).
3. Post operative sedation score was assessed using the Four Point Sedation Score
4. Patient was evaluated for any other side effects like Pruritis, Nausea and vomiting, Urinary retention, Headache, Local hematoma and Motor block.

Post operative IV fluids were continued till patients were allowed orally.

Data Analysis & Results

The data was collected on a standard Proforma and tabulated. The data for continuous variables was analyzed in terms of Mean and Standard Deviation or Median with Interquartile Range. The Statistical significance of different variables was determined by Student's t- test/ non parametric Wilcoxon's Mann Whitney test as appropriate. The Chi- square/ Fisher exact test was applied for categorical variable. Statistical significance was determined at p- value < 0.05.

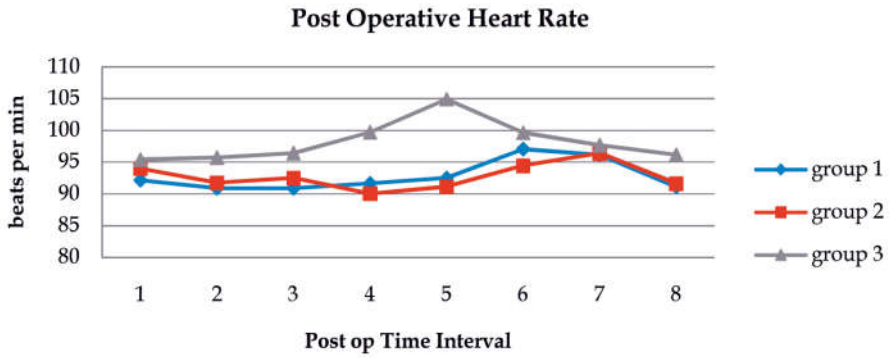
Baseline demographic parameters viz age (years), body weight(kg) and duration of surgery (min) of all three Groups was similar to each other. There is significant increase in post operative heart rate in Group 3 compared to Group 1 &2 at T2 (p=0.011) and T4 (p=0.000). Post operative heart rate in Group 1 &2 were comparable at all times. There is a significant increase in post operative mean arterial pressure in Group 3 compared to Group 1 & 2 at T4 (p= 0.046) and there is a significant increase in post operative mean arterial pressure in Group 1 compared to Group 2 & 3 at T8(p= 0.045). There is a significant increase in post operative respiratory rate in Group 3 compared to group 1 & 2 at T4(p=0.031) and there is a significant decrease in post operative respiratory rate in Group 3 compared to Group 1 & 2 at T8 (p= 0.001). Post operative respiratory rate of Group 1 &2 was comparable at all times.

Post operative analgesia as assessed by median of MOPS score showed that there was significant increase in Group 3 at T4 {5 (0-8)} as compared to Group 1{2 (0-6)} and group 2 {2(0-5)}. The median post operative sedation score from T0-T1 was highest in Group 2 as compared to Group 1 & 3 in which it was comparable. The total no. of rescue analgesics given in group 3 (46) was highest in comparison to Group 1 (22) & 2 (20).

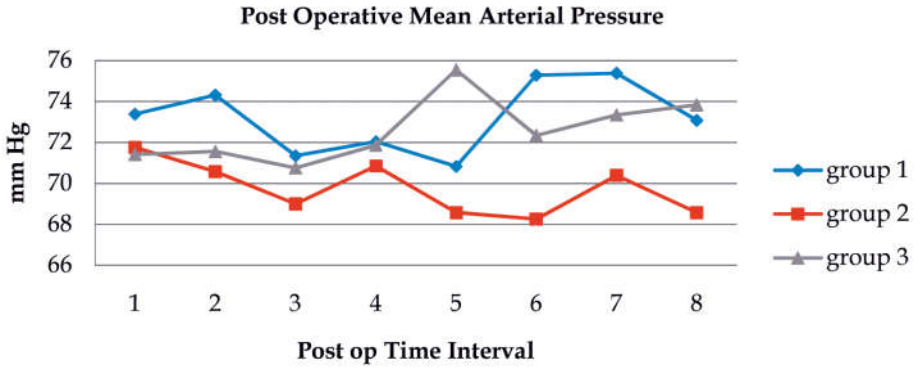
There was significant difference in the duration of analgesia between Group 1 and 3 and between Group

Table 1: Demographic distribution

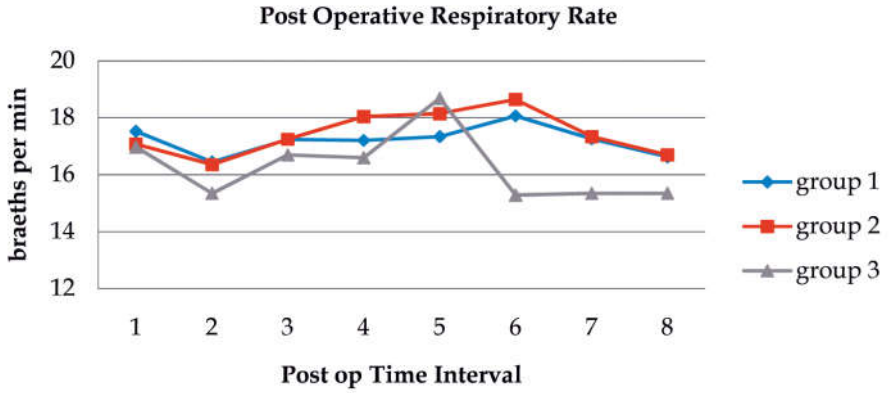
	Group 1	Group 2	Group 3	p-value
Age(years)	4.28±2.170	4.79±2.061	4.31±2.316	0.620
Weight(kg)	13.66±3.467	15.36±2.725	14.59±3.176	0.128
Duration of surgery (min)	38.55±13.341	35.89±12.914	36.55±17.066	0.773



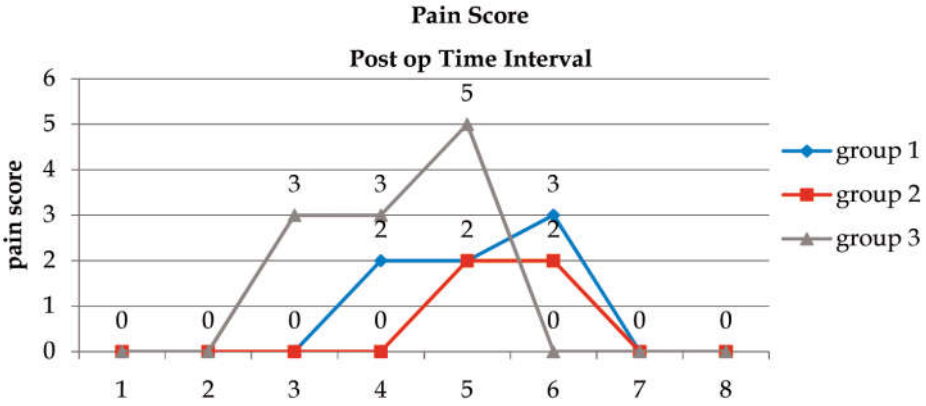
Graph 1: Comparison of Post operative heart rate in three groups



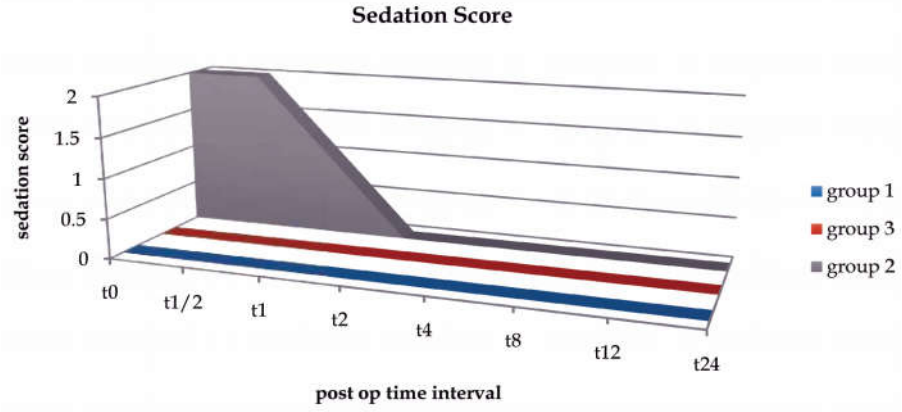
Graph 2: Comparison of Post operative Mean arterial Pressure in three groups



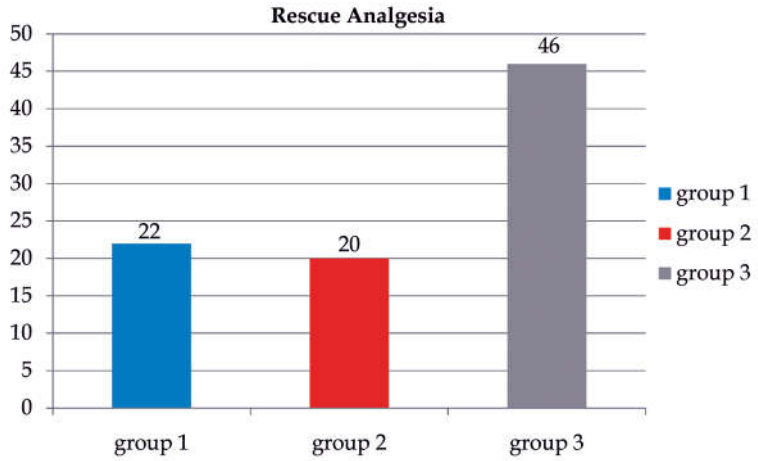
Graph 3: Comparison of Post operative Respiratory rate in three groups



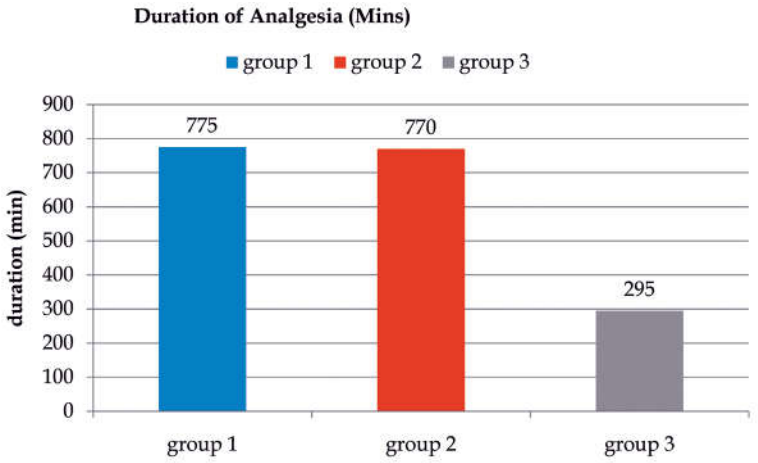
Graph 4: Comparison of Post operative Pain score in three groups



Graph 5: Comparison of Post operative sedation score in three groups



Graph 6: Comparison of rescue analgesia required in three groups



Graph 7: Comparison of duration of analgesia in three groups

2 and 3. ($p<0.05$). There was no significant difference in the duration of analgesia between group 1 and 2. ($p>0.05$).

Discussion

Caudal analgesia is a relatively simple technique with a predictable level of blockade, and is by far the most common regional anaesthetic used in paediatric surgery for lower abdominal, urological and lower limb surgery [1,2,9].

Clonidine, an α_2 adrenergic agonist produces analgesia without significant respiratory depression after epidural administration. Clonidines' analgesic effect is more pronounced after neuraxial injection, due to its action on spinal cord of inhibiting release of nociceptive neurotransmitters, and makes this route of administration preferable. The addition of clonidine prolongs the duration of action of bupivacaine after intrathecal and epidural administration in both children & adults (Klimscha 1995) [1].

Several authors have used clonidine as an adjuvant to 0.25% bupivacaine for caudal block in children with variable results [1,9,10,11,12]. In children, a mixture of 1 ml of 0.25% bupivacaine with 1-2 µg/kg clonidine significantly improves the duration and quality of caudal analgesia [1,9,12,13,15,21].

Although the results of different studies showed that clonidine when added to 0.25% bupivacaine for paediatric caudal analgesia prolonged the duration and improved the quality of post operative analgesia, the results differed widely. Moreover, clear advantages & disadvantages, if any, of the different doses of clonidine used, could not be ascertained. In an attempt to find out the optimal doses of caudal clonidine in children, we designed a double blind randomized controlled trial to comparatively evaluate the efficacy of bupivacaine with two different doses of clonidine for paediatric caudal analgesia in infra-umbilical surgeries.

In our study, the type of surgeries performed were mainly Herniotomies (n=34), Urethroplasties (n=23) and post burn split skin grafting (n=14) with others being Orchiopexy (n=6), phimosis(n=2), anal stenosis (n=3), Z- plasty (n=2) and cysto-lithotomy (n=2). All the three groups were comparable with respect to type of surgeries. The type of surgeries in the study groups of Klimscha et al [1] (hernia repair), Jamali et al [10] (sub-umbilical surgeries), Archna Koul et al(inguinal hernia repair) [13], Hennawey et al (lower abdominal surgeries) [8] and Parmeshwari et al (sub umbilical surgeries) were similar to our surgeries [11].

In our study, no statistically significant differences were observed between the three groups regarding intraoperative heart rate, mean arterial pressure, systolic blood pressure, diastolic blood pressure, respiratory rate, SpO_2, and $EtCO_2$,. All the three groups were comparable.

Post operatively, patients' vital parameters were monitored for 24 hours at time interval of 0, ½, 1,2,4,8,12 and 24 hours. The vital parameters monitored were heart rate, mean arterial pressure, respiratory rate, SpO_2, pain score, sedation score and duration of analgesia.

Efficacy of post operative analgesia assessed by MOPS score was found to be better in group 2 followed by group 1 and least in group 3. The distribution showed that median score of pain was highest in group 2 at T8 (Median 2 range 0-5) with maximum patients requiring analgesia between T4 to T8 i.e. between 4 to 8 hours post operatively. In group 1, the median score of pain was maximum at T8 (median 3, range 0-6) while for group 3 median score of pain was maximum at T4 (median 5 range 0-8). The reason for this is a shorter duration of analgesia i.e. 4 hours, for plain bupivacaine, used in group 3.

Duration of analgesia was assessed by the time from giving the caudal block to the first rescue analgesic. The median duration of analgesia (min) from application of caudal block to first rescue analgesic given to patients post operatively was 775min, 770 min and 295 min in group 1,2 and 3 respectively. There was a significant difference in the duration of analgesia between group1 and group3 and between group 2 and 3 but there was no significant difference between group 1 and 2. Klimscha too had shown in an earlier study that duration of analgesia was significantly longer {$p<0.05$} in bupivacaine and clonidine 1 µg/kg group and bupivacaine and clonidine 2 µg/kg group {median 360(range270-360)min.}and {median 360(355-360)min.} respectively, compared with the placebo {77(45-190)min.}, bupivacaine 0.25% {346(105- 360)min.} or bupivacaine & epinephrine group {300(75-360)min.} [1] . Similarly B. cook had shown that the median duration of caudal analgesia was 5.8 hr in bupivacaine with Clonidine 2 µg/kg group [13]. The variability in the duration of caudal analgesia in the above two studies as compared to our findings could be due to the fact that they used parental assessment for acute paediatric pain which is less objective than the ratings of professional health care providers. J J Lee et al had shown that the mean duration of caudal analgesia for clonidine 2 µg/kg was 588±150 min [9] and Aruna Prameswari had shown the mean duration of analgesia to be 593.4± 423.3 min for caudal clonidine 1µg/kg group [11] both of which are similar to our results.

There were significantly higher number of rescue analgesics required in Group 3 (n=46) as compared to Group 1 (n=22) and Group 2 (n=20). All the patients in Group 3 required post operative analgesia, however, 31% patients in group 1 and 28.5 % in Group 2 did not require any rescue analgesic for 24 hours. This result is supported by findings of Jamali et al who found that 46% of patients in clonidine group (1µg/kg) required no post operative pain medication as compared to 13% in control group during the first 24 hours after caudal Anaesthesia [7]. J J Lee in his study had shown that children in bupivacaine group were given 26 & 40 administrations of morphine & paracetamol respectively for 24 hrs and children in bupivacaine with clonidine 2 µg/kg group had a total of 16 & 29 administrations of morphine & paracetamol respectively for 24 hrs [9]. Similarly, Helmut Hegar found out that within 24 hr post operative period 16% of children in clonidine 1µg/kg and clonidine 2µg/kg Group required additional analgesia as compared to ketamine Group in which 63% of children required additional analgesics [6]. These studies therefore support our findings that clonidine 1µg/kg and 2µg/kg Group require less number of rescue analgesics as compared to Control Group.

In our study, the sedation score for 65% of patients in Group 1 was 0(score being 1 for 14 % and 2 for 17% of patients). The sedation score for 67% patients in Group 2 was 2 (score being 0 for 18% and 1 for 14% patients). The sedation score for 96% of patients in Group 3 was 0 (score being 1 for 4% of patients only). The above sedation scores were observed at immediate post operative period i.e. within 2 hours after surgery. Similar results were obtained in previous reports by Lee and Rubin who demonstrated a longer duration of post operative sedation following caudal bupivacaine with clonidine 2µg/kg [9]. They found that the mean duration of sedation in the immediate post operative period and before supplementary analgesia

was required were 5.8 hr and 9.1 hr for plain bupivacaine group and bupivacaine with clonidine (2μg/kg) group respectively. The longer duration of sedation in the clonidine group resulted partly from the sedative effect of clonidine and partly from longer duration of analgesia provided by clonidine. The sedative hypnotic effects of α_2- adrenergic agonists are related to the inhibition of neural firing in the locus coeruleus, a brainstem nucleus located in the dorsal part of the medulla [22]. This supraspinal effect is logical after systemic administration of clonidine. Ivani et al reported that sedation was present in all children who received a lumbar epidural injection of 2μg/kg clonidine and suggested that clonidine sedation is dose dependent [14]. Patients were evaluated for different side effects and none of the patients showed features of pruritis, headache, local hematoma and motor block post operatively. Nausea and vomiting was seen in three patients of Group 2. Similar results were reported by Joshi et al and Archna Koul et al [10], which were that since the patients who underwent Urethroplasty were cauterized, so urinary retention could not be assessed but overall there were two patients in Group 2 and one patient in group1 who showed signs of urinary retention.

No untoward effects in terms of motor weakness, hematoma, hypotension, or bradycardia were seen in any of the patients. Three patients developed urinary retention while two patients had nausea & vomiting.

Conclusion

To conclude, we recommend a dose of 1μg/kg clonidine as an adjuvant to 0.25% bupivacaine (0.75ml/kg) for infra-umbilical surgeries to significantly prolong post-operative analgesia without causing significant sedation. Increasing the dose of clonidine to 2μg/kg didn't significantly prolong postoperative analgesia but did produce significant sedation, which might interfere with discharge criteria for day care surgery.

Acknowledgement

The study was approved by research and ethical committee of Safdarjung Hospital & VMMC, New Delhi. Dinesh Panwar and Nikki Sabharwal wrote the manuscript and developed the idea of research study.

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