EFFICACY OF CAUDAL BUPIVACAINE ALONE OR IN COMBINATION WITH CLONIDINE OR NEOSTIGMINE FOR POSTOPERATIVE ANALGESIA IN PAEDIATRIC PATIENTS UNDERGOING ELECTIVE HERNIOTOMY

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Summary

Various drugs have been used as adjunct to caudal bupivacaine for postoperative pain relief in paediatric patients with variable results. This randomized prospective study was designed to assess and compare the efficacy of clonidine and neostigmine used as an adjunct to bupivacaine for caudal analgesia in paediatric patients. Seventy five patients undergoing elective inguinal herniotomy were included in one of the three following groups. Group B patients received 1 ml/kg of 0.25% bupivacaine caudally. Group C patients received 1 ml/kg of 0.25% bupivacaine and 1 µg/kg clonidine. Patients of group N were given1 ml/kg of 0.25% bupivacaine and 2 µg/kg neostigmine. Postoperative analgesia was assessed by CRIES scale.
The mean duration of analgesia was 5.92±0.6 hours in group B, 11.17±0.88 hours in group C and 13.16±0.46 hours in group N. The prolongation of duration of analgesia was significant in both Group C and N in comparison to group B. Occurrence of adverse effects was statistically insignificant among the three groups.
The addition of both clonidine and neostigmine with bupivacaine administered caudally significantly increases the duration of analgesia. However, neostigmine causes more prolonged analgesia than clonidine.

Key words*:* Clonidine, Neostigmine, Bupivacaine, Caudal analgesia.

Introduction

Pain is probably the most feared symptom, which human being always tries to alleviate and conquer. It is defined by the international association for study of pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[1]. Optimum pain relief is a big challenge in paediatric patients. It is very much difficult to differentiate restlessness or crying due to pain from that of hunger or fear in children. An effective pain therapy to block or modify the myriad physiological responses to stress has become essential component of modern day paediatric anesthesia practice.

Single shot caudal epidural block provides excellent analgesia during immediate post operative period following infraumbilical surgeries, but patients often feel significant pain after the regression of block. Many attempts have been made to prolong the duration of analgesia by using adjuvants to local anaesthetic agent.

Clonidine is an imidazoline derivative with alpha$_2$ agonist activity. When administered in the epidural space or intrathecally, clonidine has a substantial antinociceptive effect by its action on the alpha$_2$ receptor in the dorsal horn of spinal cord and brain stem nuclei implicated in pain[2, 3]. Clonidine administered as an adjunct with bupivacaine, prolongs the duration of analgesia. The sedative property of clonidine reduces the requirement of hypnotics and is often a desirable feature [4].

Neostigmine inhibits the breakdown of acetylcholine which has been shown to produce analgesia[5]. It blocks the activity of both true and pseudo-cholinesterase, and thereby enhancing the accumulation and binding of acetylcholine at various cholinergic sites responsible for analgesia[6]. There are several cholinergic receptors in the spinal cord such as μ and δ opioid receptors and alpha$_2$ adrenoceptors. Increased accumulation of acetylcholine at these receptor sites may produce analgesia[7].

The study was conducted to compare the efficacy of clonidine and neostigmine as an adjunct to bupivacaine to provide postoperative pain relief in paediatric patients.

Methods

The study protocol was approved by the Institutional Ethical Committee of Calcutta National Medical College and Hospital and informed consent was taken from the guardians. Seventy five ASA grade I paediatric patients, aged between 1-6 years undergoing elective inguinal herniotomy were included in our study. Patients with neurological deficits, neurological diseases, skeletal deformities and bleeding disorders were excluded from our study.

Patients were randomly assigned to one of the three groups. Group B patients received 1ml/kg of 0.25% bupivacaine and 0.2ml of 0.9% of saline (using a tuberculin syringe) administered caudally. Group C patients received 1ml/kg of 0.25% bupivacaine and 1μg/kg clonidine (making a volume of 0.2 ml with addition of distilled water using a tuberculin syringe).Group N patients received 1ml/kg of 0.25% bupivacaine and 2 μg/kg neostigmine (again making a volume of 0.2 ml with addition of distilled water with the help of a tuberculin syringe). Solutions were prepared by an anaesthesiologist, who was totally unaware of the nature of the study.

Patients were premedicated with oral midazolam (0.5mg/kg) mixed with honey 30 minutes before anaesthesia. On arrival in the operation thaetre, routine monitors (ECG, pulse oxymetry, NIBP) were attached and baseline vital parameters like heart rate, mean arterial blood pressure (MAP) and arterial oxygen saturation (SPO_2) were recorded. Induction was done by increasing concentration of halothane (0.5-3%) along with oxygen and nitrous oxide mixture (40:60) through ayres T piece with Jackson Rees modification and facemask. After induction, an intravenous line was secured. Inj vecuronium 0.1mg/kg was administered to facilitate endotracheal intubation with appropriate size endotracheal tube. Anaesthesia was maintained with 60%, nitrous oxide in oxygen and 0.5% halothane using mechanical ventilation. The patients were positioned in left lateral position. After aseptic draping, a 23G needle was introduced into caudal space and either bupivacaine with saline (Group B) or bupivacaine with clonidine (Group C) or bupivacaine with neostigmine (group N) was administered. At the end of the operation, residual neuromuscular block was reversed by appropriate dose of neostigmine and atropine and tracheal extubation was performed. Heart rate, MAP and SPO_2 were recorded throughout the operation at an interval of 5 minutes. In PACU, vital parameters, severity of pain and sedation was recorded at an interval of one hour.

Pain was assessed by CRIES scale [8] (Table1). A score of 0 signifies excellent analgesia whereas a score of 10 indicates that analgesia is ineffective. Patients were given rescue analgesia (syrup paracetamol) when pain score is 4 or more.

Table 1: CRIES Scale

	0	1	2
Crying	No	High pitched	Inconsolable
Requires O_2 for $SPO_{2>95\%}$	No	< 30% of O_2	> 30% of O_2
Increased vital signs	No increase in HR Or MAP	Increase in HR MAP < 20%	Increase in HR MAP >20%
Expression	None	Grimace	Grimace / Grunt
Sleepless	No	Wakes at frequent Intervals	constantly awake

Sedation was assessed by 4 point scale.

1. Barely arousable (sleep, needs shaking or shouting to arouse)
2. Asleep (eyes closed, arousable with soft voice or light touch)
3. Sleepy (Eyes open but less active and responsive)
4. Awake

Statistical analysis:

Statistical analysis was performed by a computer programme; Statistical Product for the Social Sciences (SPSS version11.5). The results are expressed in Mean ± SD, Comparison between groups were performed by the Kruskal-Wallis one way ANOVA by ranks or Fisher's exact test for small samples with a 5% risk. Mann-Whitney-Wilcoxon tests were performed when normality tests failed.

Results:

The groups were comparable with respect to age, weight and duration of surgery (P>0.05) (Table 2).

Table 2: Patients Characteristics (Mean ± SD)

	Group B (n=25)	Group C (n=25)	Group N (n=25)	P value
Age (yrs)	4.25 ± 1.32	4.77 ± 1.92	4.47 ± 1.72	0.47
Weight (kg)	18.45 ± 4.15	17.8 ± 2.79	17.11 ± 3.36	0.52
Duration of surgery (mins)	39 ± 9.6	37 ± 7.8	40 ± 7.73	0.58

In all the groups, there was no significant change in the heart rate and MAP from the baseline Value in intra-operative and postoperative period (P > 0.05) (Table 3).

Table 3: Change in haemodynamics (Mean ± SD)

	Group B	Group BC	Group N	P value
Preoperative HR (bpm)	97.26 ± 10.5	92.23 ± 10	95.32 ±9.24	0.08
MAP (mm Hg)	75.33 ± 6.85	78 ± 7.14	76.12±8.38	0.16
Intraoperative HR (bpm)	98 ± 10.5	94.2 ± 8.6	97.26±7.6	0.7
MAP (mm Hg)	78.13 ± 5.44	80.63 ± 5.28	78.52 ± 6.88	0.09
Postoperative HR (bpm)	94 ± 9.6	90 ± 8.13	92±10.4	0.8
MAP (mm Hg)	72.23 ± 4.87	69.86 ± 5	70.82±4.64	0.079

Duration of postoperative analgesia was significantly prolonged in Group C (11.17±0.88 hours) and Group N (13.16±0.46 hours) in comparison to Group B (5.92±0.6 hours). P value was determined by comparing control (B), clonidine (C) and neostigmine (N) groups ($p < 0.05$) (Table 4).

Table 4: Duration of analgesia (Mean± SD).

Duration of analgesia (hours)	Group B	Group C	Group N	P value
	5.92 ± 0.6	11.17 ± 0.88 *	13.26±0.46 *	0.00

* Significant difference within groups (P<0.05)

After one hour, most of the patients had sedation score 2 in all the groups whereas after six hours, maximum number of patients had sedation score 3 (in all the groups). At twelve hours, patients of all three groups mostly had sedation score 4. Sedation scores were comparable between the groups. (Table 5)

Table 5: Sedation Score in Post-operative period in hours [No of Patients (%)]

Post Operative Period (hrs)	Sedation Score 1			2			3			4		
	GrB	GrC	GrN	GrB	GrC	GrN	GrB	GrC	GrN	GrB	GrC	GrN
1	0	0	0	19 (76%)	21 (84%)	20 (80%)	3 (12%)	2 (8%)	2 (8%)	3 (12%)	2 (8%)	3 (12%)
3	0	0	0	14 (56%)	12 (48%)	15 (60%)	6 (24%)	6 (24%)	5 (20%)	5 (20%)	7 (28%)	5 (20%)
6	0	0	0	5 (20%)	6 (24%)	5 (20%)	14 (56%)	12 (48%)	14 (56%)	6 (24%)	7 (28%)	6 (24%)
12	0	0	0	3 (12%)	4 (16%)	2 (8%)	6 (24%)	6 (24%)	5 (20%)	16 (64%)	15 (60%)	18 (72%)

No significant difference were noted in the development of side effects, like post operative nausea and vomiting (PONV), urinary retention and respiratory depression (Table 6).

Table 6: Distribution of patients according to adverse effects (Values are in number)

Adverse Effects	Group B	Group C	Group N	Statistical Significance
Nausea and vomiting	2	2	4	P>0.05; NS
Urinary retention	0	0	0	
Respiratory depression	0	0	0	

S- Significant, NS- Not Significant

Discussion

The goal of postoperative analgesia is to relief pain as well as to inhibit trauma induced nociceptive impulses to blunt autonomic reflexes. It helps to enhance restoration of function by allowing patients to breathe and move freely[9]. Historically, children have been under treated for pain because of the wrong notion that they neither suffer or feel pain, nor respond to or remember the painful experiences to the same degree that adult did.

Amongst the various means of providing post operative analgesia, use of enteral and parenteral analgesics (both opioids and non-opioids) is associated with risks such as gastro-intestinal bleeding, precipitation of asthma, thrombocytopoenia, nausea, vomiting, sedation, respiratory depression, hepatotoxicity, nephrotoxicity etc. The regional technique including the caudal block, avoid most of the problems and it is possible to achieve a better analgesia with minimum of drug dose and minimum of complications. Caudal block is easy to perform and has been found to be very effective in children, especially in infra-umbilical surgery like herniotomy[10].

Various local anaesthetic agents (eg. lidocaine, bupivacaine, etc.) have been used for caudal block. Adjuncts like opioids (morphine[11], butorphanol[12], etc.), clonidine[13], midazolam and ketamine[14] are added to local anaesthetic agents to increase the duration of analgesia, decrease the individual dose of the drug and hence decrease the side effects[15].

Clonidine has been found to be an effective additive to bupivacaine in caudal block. Addition of clonidine has been found to increase the duration of analgesia without any increase in the side effects[16]. When administered in caudal space, clonidine produces analgesia by interacting with $alpha_2$ adrenergic receptors. These receptors are located on the superficial laminae of spinal cord and brain stem nuclei implicated in pain, so analgesia can be produced at peripheral, spinal and brain stem sites[2, 3]. In our study, we used clonidine in the dose of 1µg/kg and did not observe significant incidence of side effects like bradycardia and hypotension. Lee JJ and Rubin AP[17] administered clonidine in a dose of 2µg/kg along with bupivacaine in children undergoing orthopaedic surgery in their study. They observed higher incidence of bradycardia and hypotension associated with higher dose of clonidine. Although they found significant prolongations of analgesia (9.8 hours) as compared to bupivacaine alone (5.2 hours), Klimscha W and Chiairi A[4] reported that analgesic efficacy does not seem to be enhanced by increasing the dose of clonidine from 1µg/kg to 2µg/kg.

Considerable evidences exist to implicate the role of cholinergic agonists and anti cholinesterase agents in spinal inhibition of nociceptive transmission. It is postulated that there are cholinergic receptors in the spinal cord such as µ and δ opioid and $alpha_2$ adrenoreceptor type, known to selectively alter pain behaviour[7]. It is also found that intrathecal analgesia by neostigmine is mediated through M1 and M2 muscarinic cholinergic receptor stimulation[18]. Neostigmine inhibits the breakdown of an endogenous spinal neurotransmitter, acetylcholine[5]. It blocks the activity of both true and pseudo-cholinesterase and thereby enhancing the accumulation of acetylcholine at various sites responsible for analgesia[6].In our study, we used neostigmine in the dose of 2 µg/kg and found significant prolongation of analgesia (13.26±0.46 hours).

Almenrader N and colleagues[19] administered neostigmine caudally in children in a dose of 10μg/kg and although analgesic duration was 21.8 hours, the incidence of PONV was 30%. The high incidence of PONV could be due to the higher dose of neostigmine (10μg/kg). In another study by Mahajan R and colleagues[20], they used neostigmine in a dose of 2 μg/kg and observed 15% incidence of PONV. George M and colleagues[21] used neostigmine again in a dose of 2 μg/kg and noted prolongation of analgesia (15.16 hours). They used 0.1 mg/kg ondansetron in all the children towards the end of surgery and observed not a single incidence of PONV. They argued that administration of prophylactic anti-emetics was useful to negate the incidence of PONV[22] and so there is no harm in using ondansetron prophylactically. In our study, the incidence of PONV is not significant (16%). The similar or even higher incidence of PONV had been reported with the use of caudal bupivacaine alone[23] or caudal opioids[24].

We found a sedation score either 2 or more in all the patients in our study. Klimscha W and Chiairi A[4] have found lower sedation score at doses of 2μg/kg clonidine as compared to 1μg/kg. Lee JJ and Rubin AP[17] also confirmed significantly longer sedation when 2μg/kg clonidine was used. There was no incidence of urinary retention or respiratory depression in any of the patients of all three groups in our study.

Conclusion

Addition of both clonidine and neostigmine with bupivacaine administered caudally in paediatric patients significantly increases the duration of analgesia. The patients stay haemodynamically stable and there are no undue side effects. However, neostigmine causes more prolonged analgesia than clonidine.

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