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Original article

Caudal neostigmine with bupivacaine for postoperative analgesia in pediatric patient: comparison with bupivacaine alone.

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Abstract

Background: The use of caudal block in children was extensively reviewed by Kay in 1974.Its advantages are postoperative pain relief,decrease need for narcotic and non-narcotic analgecics,early feeding ,early ambulation,less risk of chest infection,more rapid return of child's bright and alert state and early discharge from hospital.

Material Method: We studied 75 children, ASA physical status 1 or 2, aged 2-10 yrs., undergoing elective surgery below the level of umbilicus. Patients were allocated randomly to one of the three groups (n=25).Group B received caudal Inj.of 0.25% bupivacaine 1ml/kg, Group BN1 received 0.25%bupivacaine 1ml/kg with Neostigmine 1mcg/kg, Group BN2 received 0.25% bupivacaine 1ml/kg with neostigmine 2mcg/kg. Total volume was kept same in all the groups. HR, BP, RR were monitored continuously intraoperatively and 2 hrs. after surgery in recovery room. Post-operative pain was assessed at 30 min, 2, 4,8,12 and 24 hrs after recovery from anaesthesia using modified objective pain score. A postoperative score $\geq$ 4 was managed with a paracetamol suppository (15mg/kg), The time at which postoperative rescue analgesia, if any,was first received and number of paracetamol doses per 24 postoperative hrs. were noted.

Result: Time to first rescue analgesic administration was longer in group BN1 and BN2 than group B ($P < 0.05$). Incidence of side effects .such as nausea / vomiting was not significantly different in all three groups.

Conclusion: We concluded that addition of neostigmine to caudal bupivacaine is associated with prolonged duration of postoperative analgesia without increasing incidences of side effect than caudal bupivacaine alone.

Introduction

Pain is perhaps the most feared symptom of disease, which man is always trying to alleviate and conquer since ages. it is defined by the international association for study of pain as an "unplesant sensory and emotional experience associated with acctual or potential tissue damage or described in terms such damage".children are very special in this regard.it is also very difficult to diffrentiate restlessness or crying due to pain from that of hunger or fear in the children.

Historically children have been undertreated for pain and for painfull procceders because of wrong notion that they neither, suffer or feel pain nor responded to or rembeber to painfull experinces to the same degree that adults did.

the society of paediatric anaesthesia, at its 15th annual meeting at new orleans, Louisiana 2001 clearly defined the alleviation of pain as a basic human right" irrespictive of age and medical condition (1) .

The use of caudal block in children was extensively

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reviewed by Kay in 1974 (2). Its advantages are postoperative pain relief, decrease need for narcotic and non-narcotic analgesics, earlyfeeding, and earlyambulation, less risk of chest infection, more rapid return of child's bright and alert state and early discharge from hospital.

Caudal block offers fairly simple technique a high success rate.Many drugs including epinephrine,morphine,clonidine,ketamine,midazolam and tramadol have been co-administered with caudal bupivacaine to maximize and extend duration of analgesia.Caudal morphine may be associated with delayed respiratory depression,Caudal clonidine and midazolam have been associated with prolonged sedation.Behavioural side effects were reported with use of Caudal ketamine and increased incidence of post-operative vomiting was observed with use of caudal tramadol.This study was designed to compare analgesic efficasy and adverse effects of caudal administration of neostigmine with bupivacaine against caudal bupivacaine alone in paediatric patient undergoing elective surgery below the level of umbilicus.

Material and methods

The study was carried out at civil hospital, Ahmedabad during March 2007 to February 2008.We studied 75 children, ASA physical status 1 or 2, aged 2-10 yrs., undergoing elective surgery below the level of umbilicus.Written inform consult form were taken from all the patients.Patients with history of infection at back, pre-existing neurological or spinal diseases, congenital anomaly of lower back, bleedingdiathesis, allergic reactions to local anesthetic agents were excluded from the study.

All patients were examined a day before surgery.Pulserate,blood pressure,respiratory rate were recorded.Routine investigations like haemoglobin,renal function test,liver function test and chest x-ray were checked and recorded.Informed written concent was taken from parents. All children were kept NBM for 6 hrs.After taking patient on operating table i.v cannulation was done and inj.isolyte-P drip was started. Standard monitor like ECG,pulse oximeter and NIBP were applied.Children were premedicated with Inj.Glycopyrrolate 4 mcg/kg i.v. General anaesthesia was induced with Inj.Pentothal sodium 5-7 mg/kg i.v and orotracheal intubation facilitated with Inj.Suxamethonium chloride 2mg/kg i.v. The anaesthesia was maintained with 50% O2 +50% N2O+Isoflurane and muscle relaxation (Inj.Vecuronium or Inj.Atracurium).No intra-operative sedatives or opioids were administered.

Caudal block was performed with the patient in the left lateral position using 23 gauge short beveled needle under sterile conditions.Patients were allocated randomly to one of the three groups(n=25).Group B received caudal Inj.of 0.25% bupivacaine 1ml/kg,Group BN1 received 0.25%bupivacaine 1ml/kg with Neostigmine 1mcg/kg,Group BN2 received 0.25% bupivacaine 1ml/kg with neostigmine 2mcg/kg.Total volume was kept same in all the groups.The preparation of neostigmine used in this study was 0.5mg/ml of ampule which contains neostigmine methyl sulfate.A small elastoplast dressing was placed at site of injection in all patients.

Heart rate, Blood pressure and oxygen saturation were recorded before induction, after induction and 5 minutes after caudal anesthesia, and every 15 mins. During surgery.Adequate analgesia was defined as haemodynamic stability as indicated by absence of an increase in MAP or HR of more than 20% compared with baseline value and intraoperative requirement of inhalation agent. Isoflurane for maintenance of anaesthesia was adjusted according to haemodynamic

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parameters. I.V fluids were given according to standard regime. After completion of surgery residual neuromuscular block was reversed with Inj.neostigmine 0.05mg/kg, Inj. glycopyrrolate 0.008mg/kg. Duration of surgery was noted.

All patients were observed for 2 hrs. in recovery room before returning to the ward.HR, BP, RR were monitored continuously. Post operative pain was assessed at 30 min, 2, 4,8,12 and 24 hrs after recovery from anaesthesia using modified objective pain score. This score has five criteria. Crying, movement, agitation, posture and localization of pain. A postoperative score ≥ 4 was managed with a paracetamol suppository (15mg/kg), The time at which postoperative rescue analgesia,if any,was first received and number of paracetamol doses per 24 postoperative hrs. were noted.

Sedation score was noted at 1 hr. and 4 hr.after recovery from anaesthesia using objective score based on eye opening.(0=eye open spontaneously, 1=eye open in response to speech,2= eye open in response to physical stimulation, 3=Unarousable). The incidence of adverse events such as nausia, Vomiting, Dizziness, and Prurituswas evaluated. Respiratory depression was defined by respiratory rate <10 breaths/min.

The data were collected and statistical analysis was performed. A value of P<0.05 was considered as a statistically significant difference.

Result:

The mean age and mean weight distribution in all three groups are nearly same without any significant difference.

Table – 1: Surgical procedures

Surgery	**Group B**	**Group BN1**	**Group BN2**
Circumision	5 (20%)	5 (20%)	4 (16%)
Ing. Hernia	10 (40%)	12 (48%)	10 (40%)
Hypospadias & Urethral fistula repair	5 (20%)	2 (8%)	7 (28%)
Orchidopexy	1 (4%)	1 (4%)	1 (4%)
SPCL	2 (8%)	2 (8%)	0 (0%)
Orthopedic procedure	2 (8%)	3 (12%)	3 (12%)

This table shows that the surgeries included in this study are below the Level of umbilicus and majority of patient's undergone circumcision, herniotomy and hypospadias surgery.

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Table – 2: Intraoperative pulse rate (mean)

Intraoperative (min)	**Group B**	**Group BN1**	**Group BN2**
15	105.92	107.04	106.50
30	102.92	102.64	103.84
45	101.25	101.9	102.20
60	101.07	101.5	102.0
75	99.0	101.5	102.0
90	100.0	102.5	100.8
120	98.0	100.0	99.0

Above table shows that intraoperative (mean) pulse rate remain stable without significant fluctuation in all groups.

Table – 3: Duration of Surgery

Duration (min)	**Group B**	**Group BN1**	**Group BN2**
0-30	3	3	3
31-60	10	12	13
61-90	2	4	4
91-120	2	4	4
Mean	60.2	60.4	62.8
Sd	21.23	25.65	25.66

Duration of surgery is almost same without any significant difference as seen by mean of all the three groups. ($P > 0.05$) Majority of patients had surgical procedure for 0.5-1.5hrs.

Table – 4: MOP Score (Postoperative)

Post-operation duration (hrs)	Mean MOP Score		
0	0.88	0.96	0.88
0.5	1.32	1.12	1.08
2	2.28	1.48	1.36
4	4.08	1.84	1.86
8	4.12	2.32	2.40
12	3.92	2.88	2.88
24	4.24	4.20	4.12

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We can observe that the difference in MOP score between group B and Group BN1/BN2 become significant at 4-12hrs postoperatively. But between Group BN1 and group BN2 the difference in MOP score is not significant.

Table - 5: Onset of pain

Postoperative Duration (hrs)	Group B	Group BN1	Group BN2
0.5	0	0	0
2	0	0	0
4	18 (72%)	0	0
8	25 (100%)	0	0
12	25 (100%)	1 (4%)	0
24	25 (100%)	24 (96%)	24(96%)

As per above table majority of patients in group B felt pain at 4 hrs postoperative. But in group BN1 and group BN2 onset of pain occurs after 10-12hrs.

Table – 6: First Rescue Analgesic and No. of Rescue Analgesics

	Group B	Group BN1	Group BN2
First Analgesic (hrs)	4.12 ±0.88	19.6 ±2.44	19.96 ± 1.92
No. of Rescue analgesics			
0	0	1 (4%)	1 (4%)
1	1 (4%)	22 (88%)	22 (88%)
2	13 (52%)	2 (8%)	2 (8%)
3	11 (44%)	0	0
Mean	2.40	1.04	1.04

This shows significant difference between group B and BN1 ($P < 0.05$) but no signifficant difference in first rescue analgesic hrs.between group BN1 and group BN2 ($P > 0.05$).Group B received more doses of paracetamol than group BN1 and group BN2 to maintain adequate analgesia in first 24hrs. postoperatively.

Table – 7: Postoperative complications

Complications	Group B	Group BN1	Group BN2
Nausea/Vomiting	2 (8%)	5 (20%)	5 (20%)
Pruritus	0	0	0
Respiratory depression	0	0	0
Sedation	0	0	0

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Vomiting occurred in 2(8%). The Difference was not statiscally significant (p>0.05). Moroever,The vomiting was note severe and was effectively managed with intravenous ondansetron 0.1mg/kg. No other side effects were seen.

Discussion

There is a continuous search of newer techniques and procedures which are quick, easy and better than older ones. After successful clinical use of caudal block several studies pain relief in paediatric patients.The present study demonstrated that caudal neostigmine in dose of 1 µg/kg and 2µ/kg co-andministered with 1ml/kg of bupivacaine 0.25% markedly prolonged postoperative analgesia and reduced the need for paracetamol in children undergoing elective surgery below the level of umbilicus.

The neuroaxial administration of neostigmine is known to produce analgesia and chronic pain(3-16).Analgesic effect of caudal neostigmine observed in the present study may be attributed to the direct action at spinal cord level after transdural diffusion to the cerebrospinal fluid. Spinal delivery of the cholinesterase inhibitor neostigmine inhibits the breakdown of the endogenous spinal neurotransmitter, acetylcholine, which has been shown to produce analgesia. Neuroxial administration of neostigmine increases the concentration of acetylcholine in cerebrospinal fluid and produces

Antinociception in animal which is blocked by the intrathecal via spinal muscarinic M1 receptors and supraspinal muscarinic shown muscarinic binding in substantia gelatinosa and to a lesser extent, in laminae III and V of the dorsal horn of spinal cord. Coincident with opioids and adrebergic sites. Nakayama et al(10) in 2001 have studied analgesic effect of epidural neostigmine after abdominal hysterectomy. They found 10µ/kg epidural neostigmine combined with bupivacaine provides a longer duration of analgesia than epidural bupivacaine alone. Turan et al (16) in 2003 have studied analgesic effect of caudal ropivacaine and neostigmine. They found that group II (caudal ropivacaine + neostigmine) had prolonged period of analgesia (19.0 ± 5.54) as compared to group I (caudal ropivacauine) (7.1 ± 5.7hrs.). Our study also shows similar results.

Table – 1: Duration of analgesia in hrs.

Turan et al (16)		Our study		
Group I	Group II	Group B	Group BN1	Group BN2
7.1 ± 5.7	19.2± 5.5	4.12 ± 0.88	19.6 ± 2.44	19.96 ± 1.92

Further, Turan et al(16) had found incidence of nausea/vomiting was 3 patients `1in group II and I patients in Group I. No other side effects were seen. The incidence of nausea / vomiting was statistically insignificant. In our study, the incidence of nausea / vomiting between group B and group BN1 / group BN2 also insignificant. Also we did not found any other adverse effect.

Mohamed Abdulatif et al(9)have studied analgesic efficacy of caudal neostigmine, bupivacaine and a mixture of both drugs. They found that the time from recovery to first analgesic were longer in caudal bupivacaine + neostigmine group (22.8 ± 2.9 hrs.)

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than in caudal bupivacaine (8.1 ± 5.9hrs) (p< 0.0001).

Our study also shows similar results.

Mohamed Abdulatif et al (9) found that vomiting in caudal bupivacaine + neostigmine was 25% and in caudal bupivacaine was (10%). Postoperative vomiting was not severe and effectively managed with a single dose of IV ondansetron [242] . In our study incidence of nausea / vomiting was 8%, 20% and 20% in group B, group BN1 and group BN2 respectively which was not severe. So our study also have similar results.

Table – 2: Postoperative nausea / vomiting

Mohamed Abdulatif et al(9)		**Our study**		
Caudal Bupivacaine	**Caudal Bupivacaine + Neostigmine**	**Group B**	**Group BN1**	**Group BN2**
10%	25%	8%	20%	20%

Lauretti et al(4) found epidural neostigmine (1.2 or 4μ/kg) in lidocaine produced dose independent analgesic effect and a reduction in postoperative rescue analgesic consumption without increasing the incidence of adverse effects.

Our study also shows that caudal neostigmine produces dose independent analgesic effect and a reduction in postoperative rescue analgesic consumption. The mean postoperative pain free hrs. was 19.6 ± 2.44 in group BN1 and 19.96 ± 1.92 in group BN2 (P> 0.05). Further total no. of rescue analgesics were 1.04 in group BN1 and 1.04 in group BN2 (> 0.05). The difference was statistically insignificant.

Previous studies by Abdulatif et al(9) Turan et al(16),Lauretti et al (4) with 2ug/kg of neostigmine have not mentioned any behavioral or histological evidence of neurotoxicity from epidural administration of neostigmine with methyl and propyl of paraben as preservatives in glucose containing solution. Although preservative free neostigmine is not associated with neurotoxicity, it is no longer marketed. Therefore, we believed that the does of neostigmine used in our study would not result any neurotoxicity.

A potent advantage of central neuroaxial neostigmine is that it may counteract local anaesthetic induced hypontention by inhibitory effect on the sympathetic nerve activity. In our study, the observed perioperative haemodynamic stability with use of caudal bupivacaine + neostigmine mixture supports this conention.

Despite its proven analgesic effectiveness neuroaxial neostigmine is not yet widely accepted analgesic modality through intrathecal route due to the frequent incidence of nausea and vomiting. Probably the epidural route of administration of neostigmine may prove superior to intrathecal route with respect to the incidence of nausea and vomiting. In our study, the incidence of nausea / vomiting with use of caudal bupivacaine neostigmine was 20% which was effectively managed with IV ondansetron 0.1mg/kg. A similar incidence of postoperative vomiting was also reported by previous worker(13).

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Conclusion

In a randomized study, we examined the efficacy of caudal neostigmine with bupivacaine for postoperative analagesia and compared it with caudal bupivacaine alone in 75 children aged 2-10years., undergoing elective surgery below the level of umbilicus. After the induction of general anaesthesia, children were allocated randomly into three groups (n=25). Group B received caudal injection of bupivacaine 0.25%, 1ml/kg, Group BN1 received caudal bupivacaine 0.25% 1ml/kg with neostigmine 1ug/kg and neostigmine 2mcg/kg. Monitoring of scores of pain, sedation, postoperative nausea / vomiting and other consequences were carried out.

Time to first rescue analgesic administration was longer in group BN1 and BN2 than group B ($P < 0.05$). Incidence of side effects .such as nausea / vomiting was not significantly different in all three groups. We concluded that addition of neostigmine to caudal bupivacaine is associated with prolonged duration of postoperative analgesia without increasing incidences of side effect than caudal bupivacaine alone.

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