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A comparative study between caudal bupivacaine and bupivacaine plus clonidine for post operative analgesia in children.

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Abstract:
Aims: *To compare the quality and duration of post operative analgesia, hemodynamic changes and peri operative complications, the total number of rescue analgesic doses required post operatively and the degree and duration of sedation in each group.*
Settings and Design: *Randomised Double Blinded study.*
Material and Methods: *60 children of ASA I and II, aged 2-10 years, undergoing elective infra-umbilical surgeries were randomly allocated to group A(n=30) (0.25% plain bupivacaine 1ml/kg + 1 ml Normal Saline) and Group B(n=30) (0.25% plain bupivacaine 1ml/kg + 1µg/kg clonidine + 1 ml Normal Saline). Post operative pain, duration of analgesia, time of first rescue analgesic, total number of rescue analgesic doses, hemodynamic changes, complications and sedation were recorded.*
Statistical analysis used: *Student's t-test*
Results: *The duration of analgesia in the post operative period was more in Group B (9.98±0.86)Hrs as compared to Group A(4.3±1.12)Hrs.100% patients in Group A required two or more than two rescue analgesic within 12 hrs whereas in Group B 83% patients required single rescue analgesic and 17% required two rescue analgesic, respectively. The mean sedation scores were higher in Group B as compared to Group A.*
Conclusion: *Addition of clonidine 1µg/kg to bupivacaine (0.25%) 1ml/kg for caudal block prolong the duration of analgesia in children.*
Key-words: *Paediatric patient, Post operative analgesia, Caudal block, Bupivacaine and Clonidine.*

I. Introduction

Pain is one of the most misunderstood, under diagnosed and untreated medical problems particularly in children. It is a likely reflection of myths like the child's lack of ability to perceive pain or remember painful experiences and relative lack of knowledge about age specific aspects of physiology and pharmacology and routine pain assessment.

New JACHO (joint commission on accreditation of health care organisation) regards pain as fifth vital sign and requires care givers to regularly address and assess pain.

IASP (International association for study of pain) defines pain as "An unpleasant emotional and sensory experience associated with actual or potential tissue damage or described in terms of such damage".

Post operative pain has adverse psychological effects in child. Pain can result in restless and uncooperative patient. So, it is preferable to prevent the onset of pain rather than to relieve its existence

Various multimodal techniques for paediatric pain relief have been designed. These involve regional anaesthesia with systemic analgesics, out of which the most commonly used regional block in paediatrics is caudal epidural block.

As one of the disadvantages of caudal block is relatively short duration of analgesia. Therefore, various additives eg. Ketamine, Neostigmine, Clonidine, Ephedrine, and opioids have been used to prolong the duration of analgesia provided by single injection. Ketamine has potential risk of neurotoxicity and opioids have side effects such as nausea,vomiting and respiratory depression. Clonidine , an alpha -2 adrenergic agonist is a known antihypertensive agent. Because of its sedative and analgesic effects, it is gaining popularity in anaesthesiology. Clonidine produces analgesia by interacting with alpha 2 adrenergic receptors, located on superficial laminae of spinal cord and brain stem nuclei .It does demonstrate adverse effects like sedation, hypotension and bradycardia.

Considering the above facts, We designed the present study using bupivacaine alone and bupivacaine with Clonidine in order to assess analgesic efficacy ,duration of postoperative analgesia, hemodynamic stability,post operative sedation and any adverse effects in children undergoing infra umbilical operations.

II. Materials And Methods

After obtaining approval from civil hospital ethical committee, a written informed consent was obtained from all the parents of the children who participated in this study.This study was conducted in 60 children of ASA physical status I and II, aged 2-10 years, undergoing elective infra-umbilical surgeries like herniotomy, orchidopexy, hypospadiasis repair etc during the period from 2009 -2012.

Exclusion Criteria were
1. Patients with history or evidence of infection at back
2. Allergy to drugs
3. Congenital malformations of the back
4. Preexisting neurological or spinal diseases

All these patients underwent a pre-anaesthetic check-up the day before surgery and all the routine and specific investigations were noted. The children were electively kept NBM for 6 hrs.Before surgery and prior to operation a written and informed parental consent was taken. Intravenous line was secured and inj. Isolyte P was started. Standard monitors like ECG, pulse oximeter and NIBP were applied. All children were premedicated intravenously with injection(Inj.) Glycopyrrolate 0.04 mg/kg and Ondansetron 0.1mg/kg. General anaesthesia was induced with Inj. Thiopentone sodium 5-6 mg/kg and orotracheal intubation was facilitated by Inj. Suxamethonium chloride 2 mg/kg and anaesthesia was maintained on O_2+N_2O+Sevoflurane/Isoflurane+Inj. Atracurium/ Inj. Vecuronium bromide.

As this study was double blind both groups were given according to calculated weight basis dose with equal volume of 1 ml of (clonidine or saline) to observer. Patients were randomly assigned to receive either (Bupivacaine + saline) or (Bupivacaine + Clonidine) in each group. All assessments were made by single observer in double blind fashion.

After induction, caudal block was performed with full aseptic and antiseptic precautions with patient in the left lateral position. According to the drug administered the patients were randomly allocated into 2 groups:
Group A: (0.25%) plain bupivacaine 1ml/kg + Normal saline 1ml
Group B: (0.25%) plain bupivacaine 1ml/kg + 1µg/kg clonidine in 1ml normal saline

The site of injection was dressed and the patient was turned supine. Heart rate, blood pressure, respiratory rate and oxygen saturation were recorded before induction and then immediately after caudal anaesthesia, and every 15 minutes during surgery thereafter. Adequate analgesia was defined as hemodynamic stability as indicated by the absence of an increase in SBP or HR of more than 20% compared with baseline value and from intra-operative requirement of inhalational agent. A decrease in MAP>30% was defined as hypotension and was treated with intravenous fluids/ Inj. Ephedrine. A decrease in HR>30% was considered as bradycardia and was treated with Inj. Atropine 0.01 mg/kg.

After completion of surgery, residual neuromuscular block was reversed with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.08 mg/kg. The patients were then extubated after thorough oral and ET suction.

All patients were observed for 2 hrs, in recovery room before returning to ward. HR, BP, RR were monitored continuously. Postoperative pain was assessed at 30 min, 1, 2, 4, 6, 8, 10, 12, 18 and 24 hrs.after recovery from anaesthesia using observer pain score(OPS).

OBSERVATIONAL PAIN SCORE(OPS)

BEHAVIORAL OBJECTIVES	NONE	MODERATE	SEVERE
Facial expression	1	2	3
Crying	1	2	3
Position of legs	1	2	3
Position of torso	1	2	3
Motor restlessness	1	2	3

Duration of analgesia (time from caudal block to first dose of rescue analgesic or OPS >= 12) was recorded. A postoperative rescue analgesia was given in form of paracetamol 10 mg/kg suppository. The time of first rescue analgesia received and total number of doses received in 12hrs were noted in all the groups postoperatively.

Sedation score was noted at 15 min, 30 min, 45 min, 1hr, 2hr, 4hr, 6hr, 8 hr, 10hr and 12 hrs after recovery from anaesthesia using objective score based on eye opening:

Eyes open spontaneously (score 0), eyes open in response to verbal command (score 1), eyes open in response to physical stimulus (score 2) , un arousable (score 3). The incidence of adverse effects such as nausea, vomiting, respiratory depression and sedation was evaluated. Respiratory depression was defined by RR< 10 breathes / min.

All the observations were recorded and all the results were analyzed. Statistically data were presented as mean ± S.D. Analysis was performed. A value of $P<0.05$ was considered as a statistically significant difference with unpaired students t test. Statistical software was used from Graphpad.com

III. Results

Table-1: Demographic data

Variables	Group A	Group B
Age in years		
Mean	4.43	5.27
SD	2.12	2.20
Wt. in Kg		
Mean	12.89	14.13
SD	4.05	4.23
Sex ratio		
M:F	27:3	28:2

Table-2: Surgical procedures

Surgery	Group A	Group B
Inguinal hernia	2	4
Hypospadias & urethral fistula repair	20	17
Orchidopexy	2	3
Cystolithotomy	3	3
Extrophy bladder repair	3	3

Table-3: Duration of surgery

Duration (min)	Group A	Group B
0-30	0	0
31-60	8	10
61-90	17	15
91-120	5	5
Mean	7.5	7.5
Standard Deviation	6.18	5.59

Table-4: Hemodynamic data

PREOPERATIVE VITALS(Mean±SD)	Group A	Group B	P value
Pulse	116.4± 12.34	115.6±10.10	0.7845
BP	94.33±8.65	90.86±6.84	0.0901
INTRAOPERATIVE VITALS(Mean±SD)	Group A	Group B	P value
Pulse	113.9±10.84	111±9.52	0.2754
BP	87.9±7.14	90.1±5.95	0.199
POSTOPERATIVE VITALS(Mean±SD)	Group A	Group B	P value
Pulse	106±33.16	110±9.14	0.5267
BP	88.8±6.67	89.7±6.39	0.5956

Table-5: Mean duration of caudal analgesia in hrs

	Group A	Group B	P-value
Mean duration of analgesia	4.3±1.12	9.98±0.86	<0.0001 (significant)

Table-6: Mean OPS Score(post-operative)

Post-operative duration	Mean±SD (n=30)		P-value
	Group A	Group B	
30 min	5.37±0.65	5±0	0.0028
1hr	7.2±1.4	6.33±0.59	0.0027
2hr	10±1.78	6.97±0.79	<0.0001
4hr	11.5±2.29*	8.37±0.94	<0.0001
6hr	8.43±2.84	10±0.91	0.0055
8hr	11.2±2.64	11±1.44	0.0001
10hr	8.73±3.15	12±3.30*	0.0002
12hr	11.9±1.91	7±2.58	<0.0001
Mean OPS Score	9.29±0.76	8.33±1.02	0.0001

Table-7: No of Rescue Analgesics required

No of rescue analgesic	Group A	Group B
0	0	0
1	0	25(83%)
2	2(7%)	5(17%)
3	25(83%)	0
4	3(10%)	0

Table-8: Mean post-op sedation Score

Post-op duration	Mean±SD		p-value
	Group A	Group B	
15 min	1.2±0.4	1.53±0.56	0.0110
30 min	1.13±0.34	1.43±0.49	0.0078
45 min	1.1±0.3	1.47±0.5	0.0010
1hr	1.13±0.34	1.47±0.5	0.0032
2hr	0.73±0.51	1.2±0.54	0.0010
4hr	0.73±0.57	1.13±0.5	0.0054
6hr	0.03±0.18	1.33±0.65	<0.0001
8hr	0.03±0.18	1.23±0.49	<0.0001
10hr	0.03±0.18	0.07±0.25	0.479
12hr	0.03±0.18	0.03±0.18	1
	0.61±0.13	1.09±0.13	<0.0001

Table-9: Post operative complications.

Post-op complication	Group A	Group B
Nausea and vomiting	3(10%)	9(30%)
Respiratory depression	0	0

IV. Discussion

Clonidine is an α_2 adrenoreceptor agonist, the analgesic action of intrathecal or epidural clonidine results from direct stimulation of pre and post synaptic α_2 adrenoreceptors in the dorsal grey mater of spinal cord thereby inhibiting the release of nociceptive neurotransmitters.This effect correlates with the concentration of clonidine in the cerebrospinal fluid but not that in the plasma.

The present study was undertaken to assess the efficacy and safety of Clonidine with Bupivacaine in paediatric patients undergoing infra umbilical surgeries under caudal analgesia.

Sharpe et al[23] speculated that small volume of bupivacaine (0.5ml/kg) may not be enough to deliver clonidine upto the spinal cord leaving only direct action on the nerve routes in caudal area.These findings

suggest that the addition of clonidine 2µg/kg to low volume of caudal anaesthetics has limited clinical benefit in children undergoing circumcision.Also Joshi et al[12] in their study did not recommend the addition of 2µg/kg clonidine to 0.125% bupivacaine 1 mg/kg.So we chose a standard dose of 1ml/kg 0.25% bupivacaine in both the groups.

The dose of clonidine for epidural administration is 1-5µg/kg.we chose a dose of 1µg/kg in our study as there were studies(Klimscha et al.[14]) showing that increasing the dose from 1µg/kg to 2µg/kg did not enhance the analgesic effect of clonidine but increased the incidence of side effects like respiratory depression, bradycardia and hypotension with increasing dose.

We chose the OPS score to evaluate post operative pain as it is easy to use, is validated and gives an objective evaluation.

Demographic Data

The mean age, weight and the duration of surgery were same in both the groups.

Surgical Procedure And Duration Of Surgery

Majority of patients had surgical procedures like inguinal hernia, hypospadias, orchidopexy and was comparable in between the groups. Duration of surgery was also similar in both the groups and statistically not significant.

Intra And Post Operative Pulse Rate And Blood Pressure

In children, clonidine 1-5µg/kg has been used without clinically important respiratory or haemodynamic effects. Although haemodynamic side-effects appear to be less pronounced in children than in adults, they may be dose dependent, as reported by Motsch and colleagues [18]. They found that although heart rate and systolic pressure did not differ between groups during surgery, children receiving high dose clonidine (5µg/kg) had lower systolic pressures and heart rates during the first 3 hours after surgery compared with the control group ($P<0.05$).The side effects of neuraxial clonidine administration include hypotension and bradycardia.The antihypertensive effect results from stimulation of α_2 inhibitory neurons in medullary vasomotor centre of brainstem, which leads to a reduction in norepinephrine turnover and sympathetic outflow from the CNS to the peripheral tissues. Bradycardia is caused by an increase in vagal tone resulting from central stimulation of parasympathetic outflow,as well as reduced sympathetic drive. Our study confirms the findings of haemodynamic changes as shown by other workers(Motsch [18],Aruna parameswari[2],Lt Col Upadhyay[15], Jamali S[10] and Archna Koul[1]) .There was no significant decrease in heart rate and blood pressure from the baseline with the use of clonidine with bupivacaine in caudal anaesthesia.

Duration Of Analgesia

In children a mixture of 0.25% bupivacaine with 1-2 µg/kg clonidine has shown to improve the duration and quality of analgesia provided by caudal block. Although results vary widely, the duration of analgesia provided range from 6.3 hours to 16.5 hours for 1µg/kg clonidine to 5.8 hours and 10.25 hours for 2µg/kg clonidine. Study by Motsch et al has shown a mean duration of analgesia of 20.9±7.4 hours in children receiving caudal clonidine with bupivacaine, but a dose of 5µg/kg of clonidine was used.the wide variation in the duration of action of clonidine in the various studies could be due to: doses of clonidine used, differences in premedication and volatile anaesthetic used, type of surgery, indications for rescue Analgesia, assessment of pain and statistical analysis.

The mean duration of analgesia in our study was found to be 4.3±1.12 hours for the plain bupivacaine group Vs 9.98±0.86 for the clonidine group.

Our results were similar to that of Aruna Parameswari [2] who evaluated the efficacy of clonidine added to bupivacaine in prolonging the analgesia produced by caudal bupivacaine in children undergoing sub umbilical surgeries.100 children aged 1-3 yrs were randomized to one of the two groups. Group A received caudal analgesia with 1ml/kg 0.25% bupivacaine in normal saline and group B received 1ml/kg 0.25%bupivacaine plus 1µg/kg clonidine in normal saline. Post operative pain was assessed using FLACC scale for 24 hours. The mean duration of analgesia was significantly longer in group B (593.4±423.3 min) than in group A (288.7±259.1 min). Children in group B had lower pain scores and requirement of rescue medications.

Lt .Col.K.k.Upadhyay [15]in 2005 evaluated the efficacy and safety of clonidine as an adjuvant to bupivacaine for caudal analgesia in children.50 children 6 months to 6 years of age belonging to ASA-I,II undergoing elective lower abdominal and lower limb surgeries were included. GROUP A received 0.75ml/kg (0.25% bupivacaine plain), GROUP B received 0.75ml/kg (0.25% bupivacaine +1µg/kg clonidine).The duration of analgesia in GROUP A was 5.59±0.633 hrs and in GROUP B was 10.333±0.836 hrs $p<0.05$.in both the groups there was no significant change in heart rate and blood pressure from the baseline both in intra and

postoperative period. ($p>0.05$) and there was no significant sedation in the postoperative period leading to respiratory depression.

No Of Rescue Analgesics In The First 12 Hour Post-Operative Period

In our study the clonidine group required significantly less number of rescue analgesics as compared to plain bupivacaine group. In plain bupivacaine group all patients required 2 or more than 2 rescue analgesic within 12 hours .In clonidine group 83% patients required single rescue analgesic and 17% required 2 rescue analgesic.this is in agreement with studies by J.J.Lee[11],Aruna Parmeswari[2], Archna Koul[1] and Jamali S[10].

Mean Ops Score

At OPS Score of 12, patient needs rescue analgesic.this score was reached at 4 hours in Group A(mean 11.5±2.29) and at 11hours in Group B (mean 12±3.30).This is in agreement with the study by Aruna Parameswari [2] who reported higher FLACC scores in plain bupivacaine group.

Sedation Score

In our study the period of sedation was significantly longer in children who received clonidine. However it is difficult to distinguish between sedation and analgesia,as we noticed that all children were asleep provided they were comfortable and they became restless or awake only when they were in pain and required analgesia.the greater analgesic effect of clonidine might be mistaken for sedation and vice-versa. Hence it cannot be concluded that the longer duration of sedation was caused entirely by the sedative effect of clonidine.Moreover,the addition of clonidine did not delay significantly recovery from anaesthesia. In immediate post operative period Sedation score was 1.53± 0.56 In Group B , which means patients were sedated but arousable. After eight hours the mean sedation scores in both the groups are almost same and statistically not significant. Patients were not deeply sedated (un aruosable Score -3), during the study period. The duration of sedation was very similar to the respective duration of caudal analgesia.this is in agreement with the studies of J.J.Lee[11], Archna Koul[1], Klimscha[14])Sedation after epidural clonidine results from activation of $\alpha_2$adrenoceptors in the locus coeruleus, an important modulator of vigilance. This suppresses the spontaneous firing rate of the nucleus, thereby resulting in increased activity of inhibitory interneurones such as gamma amino butyric acid (GABA)-ergic pathways, to produceCNS depression.

Post Operative Complications

The incidence of nausea vomiting was higher in children who received clonidine.9(30%) children in clonidine group complained of nausea vomiting compared to 3(10%) in plain bupivacaine group. Joshi W[12] also reported the same.At no time in this study ,was there a decrease in respiratory rate and fall in SpO_2 requiring oxygen supplementation as demonstrated by J.J.Lee[11] and Lt Col Upadhay.[15]

So, we concluded that the addition of caudal clonidine 1µg/kg to bupivacaine (0.25%) 1ml/kg prolonged the duration of analgesia in comparison to plain bupivacaine(0.25%) 1ml/kg without an increase in adverse effects in children undergoing infra umbilical surgeries.

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