COMPARATIVE RANDOMISED STUDY BETWEEN BUPIVACAINE WITH CLONIDINE AND ROPIVACAINE WITH CLONIDINE USED CAUDALLY FOR POSTOPERTAIVE ANALGESIA IN PAEDIATRIC HYPOSPADIAS SURGERY

ABSTRACT

Background

This study was conducted to compare and evaluate the caudal epidural clonidine when mixed with ropivacaine and bupivacaine in prolonging postoperative analgesia in children of Indian genotype undergoing hypospadias surgery, as well as compare the intraoperative haemodynamics using caudal bupivacaine with clonidine vs ropivacaine with clonidine. The study was also aimed at studying the side effects and the duration of post-operative pain relief of bupivacaine with clonidine v/s ropivacaine with clonidine.

Methods

This is a prospective randomised comparative study that was carried out in the Department of Anaesthesiology, KEM Hospital, Pune, over 12 months (from October 2016 to September 2017), among 56 children having an ASA Grade of II, aged between 1 to 8 years admitted for hypospadias surgery. The data gathered was cleaned using Microsoft Excel, before statistical analysis was done**.**

Results

It was observed that caudal epidural analgesic duration was more in the bupivacaine clonidine group than in the ropivacaine clonidine group. The sedation score was higher at the second hour in the bupivacaine clonidine group. The HR and mean arterial pressure values were found to be notably higher in the ropivacaine clonidine group than those in the bupivacaine clonidine group. Intraoperatively and postoperatively, there was a decrease in pulse rate and MAP but at no time did the value reach the criteria for intervention. Other side effects like postoperative vomiting, nausea, motor blockade, respiratory distress not observed in any group.

Conclusions

Bupivacaine 0.25 % 0.5 ml per kg with clonidine 1 microgram / kg via caudal route increased the duration of postoperative analgesia with no adverse effects as compared to ropivacaine 0.25 % with clonidine 1 microgram/ kg. Hence clonidine is more efficient in increasing postoperative analgesia when added with Bupivacaine as compared to ropivacaine in Indian genotype in hypospadias surgery.

Keywords

Bupivacaine, Clonidine, Ropivacaine, Postoperative Analgesia, Hypospadias Surgery

INTRODUCTION

The most common and effective paediatric regional block is single-shot caudal analgesia. Vast amount of clinical experience is required to the ease of use, reliability, and safety of the device, particularly in children more than 5 kg. Though performing the block maybe simple, like with any regional procedure, there are a few but potentially catastrophic issues that can develop. Caudal blocks with a single shot are useful for surgical treatments below the umbilicus. Higher dermatome analgesia can be attained at the cost of a higher dose of local anaesthetic.A caudal catheter can be used to provide continuous infusion or repeated medication administration, allowing the analgesia to last as long as needed. Caudal catheters are not widely used to provide repeated doses or infusions of local anaesthetic solutions, mainly due to infection concerns.

Administration of bupivacaine for caudal analgesia is a standard for pain relief. But the single-shot injection of plain bupivacaine has only a short duration of action. It has been used in different concentrations from 0.125 % to 0.375 % but no difference in duration of postoperative analgesia was found.[1] Many drugs like diamorphine, ketamine, clonidine, buprenorphine etc. are added to bupivacaine and have been found to add quality and increase the duration of postoperative analgesia.

Due to a better safety profile than bupivacaine and lesser likelihood for nervous and cardiac adverse effects, ropivacaine has been widely utilised for regional anaesthetic in adults and older children. 2

Adjuvants added to local anaesthetics has allowed for the extension of analgesia to up to 24 hours while lowering doses and hence toxicity of local anaesthetics. It also eliminates the need for an epidural catheter, which has higher risks of displacement and is more expensive.

In light of the foregoing, this study was designed to assess and compare the efficacy of caudal epidural clonidine when combined with bupivacaine and ropivacaine in children of Indian genotype undergoing hypospadias surgery.

Objectives

1. To examine the efficacy of caudal epidural clonidine coupled with bupivacaine and ropivacaine in prolonging postoperative analgesia in children of Indian genotype after hypospadias surgery.
2. To compare intraoperative haemodynamics using caudal bupivacaine with clonidine v/s ropivacaine with clonidine.
3. To compare the side effects of bupivacaine with clonidine v/s ropivacaine with clonidine and post-operative pain free duration.

MATERIAL AND METHODS

This is a prospective randomised comparative study that was carried out in the Department of Anaesthesiology, KEM Hospital, Pune, over 12 months (from October 2016 to September 2017), among 56 children having an ASA Grade of II, aged between 1 to 8 years admitted for hypospadias surgery.

Inclusion Criteria

1. Consent was obtained after giving the patient information sheet.
2. ASA grade I & II
3. Aged1 to 8 Yrs
4. Posted for hypospadias repair
5. Weight 3-20 kg

Exclusion Criteria

1. Bleeding disorder.
2. Patients with a known history of bupivacaine or ropivacaine or clonidine hypersensitivity.
3. Patients who are mentally retarded.
4. Infection at needle insertion site.

The patients were randomly allocated to two groups. Randomisation was done by making 60 envelopes, 30 envelopes of bupivacaine clonidine and 30 envelopes of ropivacaine clonidine. Patients were randomly allowed to pick up the envelope and accordingly received single-shot caudal epidural blocks with:

Group A: 0.5 ml / kg of 0.25 % bupivacaine + 1 mcg / kg clonidine
Group B: 0.5 ml / kg of 0.2 % ropivacaine + 1 mcg / kg clonidine

After a complete pre-anaesthetic evaluation that included a detailed history, clinical examination, and pertinent laboratory testing, the cases were chosen. There were no sacral malformations, skin infections, bony landmarks, motions, or previous procedures seen on the spine. Any child suspected of having an infection in the sacral region, as well as those with apparent sacral bony deformities, were eliminated from the study.

Hemograms with PT and PTT, urine-routine/microscopy, bleeding time, and clotting time were all performed. Nil by mouth was maintained for solid food - 6 hours, breast milk - 4 hours, and clear liquids - 2 hours.

Premedication was given with inj. glycopyrrolate mcg/ kg intramuscular 30 minutes before induction of anaesthesia. An IV line was secured and started inside the operating room. Multipara monitors attached to the patient and baseline vital parameters noted down. Anaesthesia was induced with injection of thiopentone 5 mg / kg IV. Endotracheal intubation was made easier by Muscle relaxant (vecuronium 0.1 mg / kg IV). After induction and before the start of surgery, the caudal block was administered. The patient was given drugs according to the group that he belonged to. In Ayre's T-piece circuit, anaesthesia was maintained with oxygen, nitrous oxide, and sevoflurane. Top-up injections of vecuronium were utilised to keep muscular relaxation going. Intravenous fluids were supplied according to the Holiday Segar formula's specifications.

Prior to surgical incision, a clinical assessment of the success of the block was done. If clinically it was found to be inadequate, anaesthesia was supplemented with IV fentanyl 2 microgram / kg and the patient was not included in the study. At the end of the surgery neuromuscular blockade was reversed

with IV inj. neostigmine 0.05 mg / kg and IV inj. glycopyrrolate 0.01 mg / kg. The patient was extubated after confirming the adequacy of spontaneous respiration and peripheral muscle tone.
For the first 2-3 hours after surgery, patients were monitored in the post-anaesthesia care unit (PACU) and then on the wards using a standard proforma for the next 24 hours. An objective pain scale score was used to determine the level of pain alleviation. 3 Rescue analgesia was administered as needed at the onset of pain, and the total duration of analgesia was recorded. Standard statistical approaches were used to tabulate and assess the study's final results for significance.

Statistical Methods[4,5,6]

Data on categorical variables is reported as n (percentage of cases), whereas data on continuous variables is presented as mean standard deviation (SD) across two research groups. For a 2 x 2 contingency table, the chi-square test or Fisher's exact probability test were used to compare categorical variables between groups. The independent sample t-test was used to determine the statistical significance of the inter-group difference in continuous variable means. Before performing a t-test on the research variables, the underlying normality assumption was checked. Before statistical analysis, all of the data was entered and cleaned in MS Excel.

P-values less than 0.05 were considered statistically significant throughout the investigation. Against each null hypothesis, all hypotheses were formed using two-tailed alternatives (hypothesis of no difference). The data was statistically analysed using IBM Corporation's statistical software for social sciences (SPSS ver 21.0) for MS Windows.

RESULTS

The age of the cases in Group A and Group B was 3.43 1.92 years and 2.73 0.98 years, respectively, with a mean standard deviation (SD) of 3.43 1.92 years and 2.73 0.98 years. The mean age distribution did not differ substantially between the two research groups (P-value > 0.05).

Cases from Group A and Group B had mean body weights of 13.1 3.4 kg and 12.0 2.3 kg, respectively. The mean body weight distribution did not differ substantially between the two study groups (P-value > 0.05).

PONV	**Group A (n = 28)**		**Group B (n = 28)**		**P-Value (A v B)**
	n	**%**	**n**	**%**	
No	28	100.0	28	100.0	0.999^{NS}
Yes	0	0.0	0	0.0	
Total	**28**	**100.0**	**28**	**100.0**	
The numbers are n. (percent of cases). Chi-square test P-values A statistically significant P-value is less than 0.05. NS stands for statistically insignificant.					
The incidence of post-op nausea and vomiting (PONV) across two study groups					
Respiratory Depression	**Group A (n = 28)**		**Group B (n = 28)**		**P-Value (A v B)**
	n	**%**	**n**	**%**	
No	28	100.0	28	100.0	0.999^{NS}
Yes	0	0.0	0	0.0	
Total	**28**	**100.0**	**28**	**100.0**	
The numbers are n. (percent of cases). Chi-square test P-values A statistically significant P-value is less than 0.05. NS stands for statistically insignificant.					

The incidence of respiratory depression across two study groups					
Motor Weakness	**Group A (n = 28)**		**Group B (n = 28)**		**P-Value (A v B)**
	n	**%**	**n**	**%**	
No	28	100.0	28	100.0	0.999^{NS}
Yes	0	0.0	0	0.0	
Total	**28**	**100.0**	**28**	**100.0**	
The numbers are n. (percent of cases). Chi-square test P-values A statistically significant P-value is less than 0.05. NS stands for statistically insignificant.					
The incidence of motor weakness across two study groups.					
Hypotension	**Group A (n = 28)**		**Group B (n = 28)**		**P-Value (A v B)**
	n	**%**	**n**	**%**	
No	28	100.0	28	100.0	0.999^{NS}
Yes	0	0.0	0	0.0	
Total	**28**	**100.0**	**28**	**100.0**	
The numbers are n. (percent of cases). Chi-square test P-values A statistically significant P-value is less than 0.05. NS stands for statistically insignificant.					
The incidence of hypotension across two study groups					
Bradycardia	**Group A (n = 28)**		**Group B (n = 28)**		**P-Value (A v B)**
	N	**%**	**n**	**%**	
No	28	100.0	28	100.0	0.999^{NS}
Yes	0	0.0	0	0.0	
Total	**28**	**100.0**	**28**	**100.0**	
The numbers are n. (percent of cases). Chi-square test P-values A statistically significant P-value is less than 0.05. NS stands for statistically insignificant.					
The incidence of bradycardia across two study groups					
Table 1					

The mean standard deviation (SD) of operation length in Groups A and B was 51.79 7.35 minutes and 51.79 7.35 minutes, respectively. The mean surgical length did not differ substantially between the two study groups (P-value > 0.05).

In comparison to Group A, the distribution of mean HR at 15 minutes, 30 minutes, 45 minutes, 1 hour, and after extubation was substantially greater in Group B (P-value 0.05 for all).

When comparing Group B to Group A, the distribution of mean MAP before induction, at the surgical incision, 30-min, 45-min, and 1-hr was substantially greater in Group B (P-value 0.05 for all).

In comparison to Group A, the distribution of mean OPS at 6- and 7-hours was considerably higher in Group B (P-value 0.05 for all).

Group A had a substantially larger distribution of mean sedation score at 2-hours than Group B (P-value 0.05).

PONV was not found in any of the 28 cases evaluated in Group A or Group B. The incidence of PONV was statistically found to be not different between the two study groups (P-value > 0.05).

There was no respiratory depression in any of the 28 instances studied in Group A, and none in any of the 28 cases studied in Group B. The incidence of respiratory depression was statistically found to be not differentbetween the two study groups (P-value > 0.05).

There was no motor weakness in any of the 28 individuals tested in Group A or Group B. The incidence of motor weakness was statistically found to be not different between the two study groups (P-value > 0.05).

None of the 28 individuals studied in Groups A and B exhibited hypotension. The incidence of hypotension wasstatistically found to be not different between the two study groups (P-value > 0.05).

In the same way, none of the 28 cases investigated in Group A and Group B developed bradycardia. The incidence of bradycardia wasstatistically found to be not different between the two study groups (P-value > 0.05).

Parameter	**Group A (n = 28)**		**Group B (n = 28)**		**P-Value (A v B)**
	Mean	**SD**	**Mean**	**SD**	
Duration of Analgesia (Mins)	480.3	34.2	424.4	28.1	0.001***
The mean and standard deviation are used to calculate the values. Independent sample t-test P-values A statistically significant P-value is less than 0.05. *** Statistically Highly-Significant P-Value 0.001					
The incidence of mean duration of analgesia across two study groups.					
Parameter	**Group A (n = 28)**		**Group B (n = 28)**		**P-Value (A v B)**
	Mean	**SD**	**Mean**	**SD**	
Rescue Analgesia (Mins)	480.3	34.2	424.4	28.1	0.001***
The mean and standard deviation are used to calculate the values. Independent sample t-test P-values A statistically significant P-value is less than 0.05. *** Statistically Highly-Significant P-Value 0.001					
The distribution of mean time to first rescue analgesia across two study groups.					
Table 2					

The mean standard deviation (SD) of analgesic duration in Groups A and B was 480.3 34.2 minutes and 424.4 28.1 minutes, respectively. Group A had a considerably larger mean duration of analgesia distribution than Group B (P-value 0.001).

The mean standard deviation (SD) of rescue analgesia was 480.3 34.2 minutes in Group A and 424.4 28.1 minutes in Group B, respectively. In comparison to Group B, the distribution of mean time to rescue analgesia was considerably higher in Group A (P-value 0.001).

DISCUSSION

Ropivacaine proved ineffective in children when used at concentrations lower than 0.2 percent, which is why we stuck to a concentration of 0.2 percent. And clonidine 1 mcg / kg, because there was no benefit to raising the clonidine dose from 1 mcg / kg to 2 mcg / kg.

Upadhyay and colleagues (7) employed 1 mcg/kg-1 clonidine as an adjuvant with 0.25 percent bupivacaine in children undergoing infra-umbilical surgery and found a considerable extension of postoperative analgesia with no noticeable adverse effects.

To achieve efficient and prolonged caudal block with a smaller dose and a lower incidence of side effects SamitaPirlokar et al. (8) chose clonidine at a dose of 1g/kg..

Duration of Analgesia

In our study, the mean duration of analgesia in Group A was 480.3 minutes and in Group B was 424.4 minutes, with a statistically significant P-value of 0.001.

Reddy M et al.9 investigated caudal block with clonidine 0.5 mcg/kg and 1 mcg/kg as an adjuvant to 0.25 percent bupivacaine 0.5 ml / kg during circumcision in 2014.

They found that the duration of analgesia in the group that got 0.25 percent bupivacaine 0.5 ml / kg with clonidine 0.5 mcg / kg was 423.50 22.86 minutes, which was less than our study, presumably due to a lower dose of clonidine. Their length was 456.00 38.52 minutes in the group that received 0.25 percent bupivacaine 0.5ml / kg with clonidine 1mcg / kg, which was slightly less than in our trial, despite the fact that the medicine and doses were the same.

This is most likely due to the fact that they utilised a different pain scale, which only had three criteria: heart rate, blood pressure, and crying. They used a pain score of 3 that was obtained as a result of rescue analgesia.

Upadhyay et al. investigated 50 children who got 0.25 percent bupivacaine 0.75 ml / kg alone or in combination with low dose clonidine 1g / kg caudally during elective lower abdomen and lower leg procedures in 2005.

Theanalgesia duration was 10.3 hours (618 minutes) in clonidine group. This was in contrast to our trial, which had substantially shoter duration of analgesia. This might be due to the comparatively larger volume of bupivacaine used. In addition, 45 minutes prior to surgery,the children were given midazolam 0.5mg/kg syrup, which caused drowsiness. Their pain assessment scale was different, which may have contributed to their longer duration of analgesia.

Hemodynamic Effects

HR

In our study, in the bupivacaine clonidine group that is group A, mean HR was preoperatively 126 bpm, intraoperatively 93.8 bpm and postoperatively 85 bpm. In the ropivacaine clonidine group that is group B, mean HR was preoperatively 127.2 bpm, intraoperatively 96.9 bpm, postoperatively 74 bpm.

The mean HR in Group B was substantially greater than in Group A, with the difference being statistically significant.

Caudal block was explored with clonidine 0.5 mcg/kg and 1 mcg/kg as an adjuvant to 0.25 percent bupivacaine 0.5 ml/kg for circumcision by Reddy M et al.

In group I (bupivacaine 0.25 % 0.5 ml / kg + clonidine 0.5 mcg / kg), mean basal HR was 131.5 ± 10.42 bpm and intraoperatively it was 106.13 ± 7.39 bpm. In group 2 (bupivacaine 0.5 ml / kg + clonidine 1mcg / kg), mean basal HR was 132.53 ± 11.28 bpm and intraoperatively it was 104.47 ± 7.16 bpm.

Although there was a fall in HR in both the groups after caudal in this study, the fall was slightly less as compared to that in our study.

This may be due to the reason that children in this study were premedicated with injection atropine 0.01 mcg / kg. However, halothane was used as the inhalational agent in this study which can cause a decrease in HR.

Mean Arterial Pressure

In our study, mean MAP readings in the bupivacaine clonidine group were 99.5 mmHg preoperatively, 87.1 mmHg intraoperatively and 82.7 mmHg postoperatively. In the ropivacaine clonidine group, readings were 101.8 mmHg preoperatively, 89.1mmHg intraoperatively and 84.2 mmHg postoperatively.

The ropivacaine clonidine group had much higher mean MAP values than the bupivacaine clonidine group, with the difference being statistically significant.
In study by Meghani et al.[10] caudal block was performed with bupivacaine 0.25 % 1 ml/kg + 1 ml normal saline in one group and 0.25 % plain bupivacaine 1 ml / kg + 1 mcg / kg clonidine + 1 ml normal saline. The mean MAP preoperatively was 90.86 ± 6.84 mmHg, intraoperatively was 90.1 ± 5.95 mmHg, postoperatively was 89.7 ± 6.39 mmHg in the bupivacaine clonidine group. There was hardly any change in MAP values in the bupivacaine clonidine group.

In contrast, we found a considerable reduction in values in the bupivacaine clonidine group in our research.This difference was probably because of a higher dose of glycopyrrolate used by them. Also, another contributory reason could be the variable use of muscle relaxant vecuronium/atracurium and inhalational agent sevoflurane / isoflurane.

Side Effects

Hypotension and Bradycardia

Due to parasympathetic predominance and inhibition of preganglionic sympathetic neurons, clonidine administered intravenously can cause bradycardia and hypotension.

In our investigation, adding clonidine as an adjuvant resulted in a small reduction in mean arterial pressure and HR in both groups. Because their hemodynamic readings did not fall below the prescribed criteria, none of the youngsters required treatment. Following surgery, there was no significant difference in HR, SBP, or DBP between the two research groups. Madhava Reddy R et al.(11), Manickam et al.12, and Priolkar S et al.(12) found similar results.
In all of these trials, Bajwah SJS et al.13, Khatavkar SS et al.14, and Laha A et al.(15) found no significant reduction in mean HR or mean arterial blood pressure.

Sedation

Sedation is caused by caudal clonidine, which is dose-dependent. Sedation is caused by the activation of alpha-2 adrenergic receptors in the locus coeruleus. CNS depression is caused by an increase in GABA secretion concentration.

Sedation was measured in our study using a sedation score. At the 2nd hour, group A had a sedation score of 2.82 while group B had a sedation score of 2.57. The distribution of mean sedation score at 2-hours was higher in Group A than in Group B, with a statistically significant difference between the two groups. In both groups, the youngsters exhibited relatively minimal drowsiness and were easily arousable. Its findings are analogous to those of Madhava Reddy R et al., Ivani G et al.16, Manickam A et al., and Bajwa SJS et al.

Motor Blockade

The motor blockage was measured using a modified Bromage scale in our study. The incidence of motor weakness was not substantially different between the two research groups. In our research, we found no evidence of motor blockage in any of the experimental groups. This is similar to the findings of Reddy M et al. and Priolkar S et al. research.
However, our findings differ from those of Khalil et al.(17) and Manickam et al., who evaluated different dosages of ropivacaine in caudal anaesthesia and concluded that 0.2 percent ropivacaine caused motor blockage in the early postoperative period. With 0.2 percent ropivacaine, Manickam et al. found motor blockage for a brief amount of time. The causes for this disparity are inexplicable.

Postoperative Nausea and Vomiting

In our study, none of the patients experienced postoperative nausea and vomiting, although they did not receive antiemetic and nitrous oxide was administered to all of them. The incidence of PONV did not differ significantly across the two study groups (P-value > 0.05). Our findings are comparable with a study by Solanki NM et al.[18] and Shukla U et al.[19]

Our results are, in contrast, to a study by Meghani Y et al. who reported incidence of nausea and vomiting in 30 % of children in the bupivacaine clonidine group, in spite of receiving injection ondansetron. However, we fail to explain this difference.

Respiratory Depression

None of the individuals in our study suffered respiratory depression. The incidence of respiratory depression was not statistically different between the two study groups (P-value > 0.05).

These findings are comparable with studies by Shukla U et al. Solanki NM et al. Adate K et al.[20] and Parameswari A et al.[21]

CONCLUSION

The bupivacaine clonidine group had a longer duration of caudal epidural analgesia than the ropivacaine clonidine group.The bupivacaine clonidine group had a higher sedation score at the second hour .

The HR and mean arterial pressure values were significantly higher in ropivacaine group than those in the bupivacaine clonidine group. Intraoperatively and postoperatively there was a reduction in pulse rate and MAP but at no time did the value reach the criteria for intervention.

Postoperative nausea, vomiting, motor blockade and respiratory depression were not seen in any of the groups.

Hence in comparision to 0.25 percent ropivacaine with clonidine 1 mcg / kg, 0.25 percent bupivacaine 0.5 ml / kg with clonidine 1mcg/kg through caudal route extended the duration of postoperative analgesia without any adverse effects. In hypospadias surgery , clonidine combined with bupivacaine is more effective than ropivacaine in extending postoperative analgesia in the indian genotype.

CONSENT

We have taken written informed consent of all the patients involved in the study.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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