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Comparison of levobupivacaine 0.25% and bupivacaine 0.25% for caudal analgesia in children undergoing herniotomy

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Keypoints

Caudal block is widely used in children; it significantly decreases the requirements of systemic anaesthetic and analgesic agents resulting in better post – operative outcome. Bupivacaine is a commonly used local anaesthetic agent for caudal blockade but is associated with cardiotoxicity and motor blockade. Levobupivacaine, an S- enantiomer of Bupivacaine has been recently introduced in the Indian market and is considered to be a safer alternative.

Abstract

Introduction

Levobupivacaine is claimed to have less cardiotoxicity and motor blockade. Our aim was to compare efficacy, motor blockade and postoperative analgesia following caudal epidural with either levobupivacaine or bupivacaine.

Materials and methods

Sixty children scheduled for inguinal herniotomy under standard general anesthesia without neuromuscular blockade and receiving 0.75ml/kg, 0.25% caudal epidural levobupivacaine or bupivacaine were observed. Caudal block was considered ineffective if any two of the following were present on application of forceps at the operative site:

1) gross movements, 2) ≥20% increase in pulse rate, 3) ≥20% increase in respiratory rate.

Significant residual motor block was defined as a Modified Bromage score of ≥ 1 at wake up and 180 minutes after caudal block. Postoperative pain was assessed using FLACC scale. Rescue analgesia was administered when pain score was ≥ 4. Parametric and qualitative data were analyzed using Students unpaired t test and Chi-X^2 test.

Results

Demographic profile and caudal block efficacy was comparable among both the groups. Incidence of residual motor blockade at wake up was 30% with levobupivacaine and 70% with bupivacaine (P = 0.004). At 180 minutes none of the patients in levobupivacaine versus 16.67% in bupivacaine group had residual motor blockade (P = 0.236). Requirement of rescue analgesia was similar in both the groups (P=0.717). There were no significant side effects in either group.

Conclusion

Either of 0.75ml/kg, 0.25% Levobupivacaine or bupivacaine provide similarly effective caudal epidural analgesia for herniotomy in children. Less residual motor blockade is an additional advantage with levobupivacaine.

Keywords: levobupivacine, caudal analgesia, motor blockade.

Introduction

Caudal block is frequently practised regional block in children for infraumbilical surgeries. It significantly decreases the requirements of systemic anaesthetic and analgesic agents resulting in better post – operative outcome. Racemic Bupivacaine is the most popular and

commonly used local anaesthetic agent for caudal blockade. It has been widely used and extensively studied over decades. Cardiotoxicity and incidence of prolonged motor blockade stimulated the need for a drug with a wider margin of safety and a similar clinical efficacy. Hence S – enantiomers of bupivacaine were isolated and synthesized.

Levobupivacaine, a pure S- enantiomer of Bupivacaine, was approved by the United States Food and Drug Administration in 1999.The rationale behind substituting bupivacaine with levobupivacaine is to reduce the incidence of unwanted motor blockade and its wider margin of safety.[1-4] Levobupivacaine has been used in western paediatric population without any untoward event and with acceptable level of motor blockade. Levobupivacaine has been recently introduced in the Indian market. To the best of our knowledge there have been no studies in the Indian paediatric population. Hence we decided to do an observational study comparing 0.75ml/kg of 0.25% levobupivacaine and 0.75ml/kg of 0.25% bupivacaine for caudal analgesia. The primary aim of the study was to determine the clinical efficacy of the caudal block during the surgery and the incidence of residual motor blockade (assessed using Modified Bromage Scale). Secondary aims were to measure the degree of analgesia (assessed using FLACC pain score), requirement of rescue analgesia, hemodynamics and side effects if any.

Materials and methods

After approval from the institutional research and ethics committee and registering the trial with the Clinical Trial Registry of India (CTRI No. CTRI/2014/06/004679), the observational study was started. Informed written consent was obtained from the parents of 60 healthy children (American Society of Anesthesiologists Class I & II) of either sex in the age group of 3 months to 6 years, scheduled for elective herniotomy.

Children with history of previous surgeries requiring handling of spinal cord, any neurological disorder, cardiac disease, pre-existing bleeding disorder, hypersensitivity to amide local anaesthetic drugs, sacral abnormalities, and local infection, were excluded from the study.

Pediatric patients receiving general anesthesia with supraglottic airway device and caudal analgesia for herniotomy were observed. In our institute all pediatric patients have intravenous access secured on the previous night. Patients were re-evaluated on the day of surgery, starvation status was confirmed and vital parameters were assessed. Inside the operation theatre monitors including cardio scope, pulse oximeter and non-invasive blood pressure were attached and lactated Ringer's solution with 1% dextrose was administered according to Holliday-Segar formula through the preexisting intravenous access. Standard pre induction drugs including Inj. Glycopyrrolate 0.004mg/kg, Inj. Midazolam 0.02mg/kg, Inj. Pentazocine 0.3mg/kg were given. Anesthesia induction was carried out with intravenous Propofol 2 – 4 mg/kg with Sevoflurane and 50% N_2O in oxygen till loss of consciousness. After achieving adequate depth of anesthesia and adequate jaw relaxation supraglottic airway device of appropriate size was inserted. Ventilation was assisted without using neuromuscular blockade and anesthesia was maintained with 50% N_2O in oxygen with Isoflurane.

After securing the airway, under all aseptic precautions caudal epidural block was performed in the left lateral decubitus position using the planned drug. Patients were divided into two groups. Group L received 0.75ml/kg of 0.25% Levobupivacaine and Group B received 0.75ml/kg of 0.25% Bupivacaine.

Surgical incision was taken approximately 15 minutes after the caudal block. Throughout the procedure vital parameters including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), Oxygen saturation (SpO_2) were monitored every 5 minutes till awakening. Parameters noted just before the performance of the caudal block were considered as the baseline parameters. Caudal block was considered ineffective if any two of the following were present on application of forceps at the

operative site: 1) gross movements, 2) ≥20% increase in pulse rate, 3) ≥20% increase in respiratory rate. At the end of surgery, supraglottic device was removed in fully awake patient with spontaneous and regular respiratory pattern, capable of maintaining airway.

In the recovery room post-operatively motor blockade was assessed at wake up, then every 15 minutes for one hour and every 30 minutes for next hour. We used Modified Bromage Scale for assessment. 0 – The patient is able to move hip, knee and ankle, 1 – The patient is unable to move hip, but is able to move knee and ankle, 2 – The patient is unable to move hip and knee, but is able to move the ankle**,** 3 – The patient is unable to move hip, knee and ankle. Significant residual motor block was defined as a motor block score of ≥ 1 at wake up and 180 minutes after caudal block.

Postoperatively, hemodynamics, respiration, motor blockade and pain were monitored in the PACU every 15 minutes for the first hour and every half hourly for next one hour. Pain was measured using FLACC scale which comprises Face(F), Leg(L), Activity(A), Cry(C) and Consolability(C). Each category was scored from 0 to 2, resulting in total score between 0 – 10, Score of 10 indicating maximum pain. Pain score ≥ 4 suggested significant pain demanding rescue analgesia. Inj. Tramadol 1mg/kg was used intravenously for rescue analgesia. The time of first rescue analgesia was noted. Later on if the patient still had pain scores of > 4 within first four hours of administration of intravenous Inj. Tramadol, then Inj. Paracetamol 15mg/kg was administered intravenously and still if the patient complained of pain then Inj. Pentazocine 0.1mg/kg was used. Parents were interviewed and the overall parental satisfaction was graded as excellent/ good/ fair/ poor.

Statistical analysis

Thirty patients were included in each group from the sample and power calculation software based on the following assumptions:

1) Difference in motor blockade of 35% between two groups (Study conducted by Breschan et al in which 60% of patients in bupivacaine group had residual motor blockade versus 25% in the levobupivacaine group); 2) Type I error of 0.05; 3) Type II error of 0.2. Statistical analysis was done using the SPSS software version 16.0.

The quantitative data like demographic profile, duration of surgery and anesthesia, hemodynamic parameters and FLACC score were analyzed using Unpaired Students't' test. Qualitative data like caudal block efficacy, post-operative motor blockade and rescue analgesia requirement was assessed using Chi X^2 test. For all the parameters, $P < 0.05$ was considered to be significant.

Results

The demographic profile was comparable among both the groups (Table 1). There was no significant difference between the groups with respect to the duration of surgery and anesthesia (Table 1). The baseline, intra-operative and post-operative hemodynamic profile was comparable and there was no statistically significant difference between the groups.

Caudal block was judged to be equally efficacious with both the local anesthetics. Only one patient in the levobupivacaine group had gross movements at incision and a significant (>20%) increase in the heart rate whereas the block in the bupivacaine group was 100% effective. On statistical analysis the difference was not significant (P = 0.313) (Table 2).

In the levobupivacaine group nine out of 30 (30%) and in the bupivacaine group 21 out of 30 (70%) patients had a significant motor blockade (Modified Bromage≥1) at wake up and the difference was statistically significant (P = 0.004) (Table 2).

None of the patients in the levobupivacaine group exhibited motor blockade at 180 min post caudal whereas five patients (16.67%) still had Modified Bromage of ≥ 1 (P = 0.236) (Table 2).

Patients having FLACC score ≥ 4 received rescue analgesia. Four patients in the Levobupivacaine group and five in the Bupivacaine group required rescue analgesia. The difference was not statistically significant (P =

0.717) (Table 2). At wake up 28/30 patients (93.3%) in both the groups were pain free, thereafter 26/30 patients (86.6%) in the Levobupivacaine group and 25/30 (83.3%) patients in the Bupivacaine group remained pain free for two hours (Table 3).

No patient in either group required further analgesia with Inj. Pentazocine and Inj. Paracetamol later on as decided by the study protocol.

There was no incidence of bradycardia, hypotension in the perioperative period. None of the patients in either group complained of postoperative nausea and vomiting. Excellent / good / fair / poor satisfaction was recorded in 83.3% / 6.67% / 10% in the levobupivacaine group and 80% / 20% of parents in the bupivacaine group. They were happy to have a calm, relaxed and pain free child in postoperative period.

Parameter	Levobupivacaine (n = 30)	Bupivacaine (n = 30)	'P' value (Unpaired 't' test)
Age (years)	3.55 ± 2.07	2.97 ± 1.86	0.267
Weight (kg)	12.56 ± 5.15	11.41 ± 3.59	0.319
Duration of surgery (minutes)	37.0 ± 13.62	39.86 ± 14.26	0.429
Duration of anesthesia (minutes)	82.0 ± 13.10	79.0 ± 14.26	0.443

Table 1. Demographic details

		Levobupivacaine (n = 30)	Bupivacaine (n = 30)	'P' value (Chi X^2)
Caudal block efficacy	Yes	29	30	0.313
	NO	1	0	
Modified bromage at wake up	0	21	9	0.004*
	≥ 1	9	21	
Modified bromage at 180 minutes	0	30	27	0.2361
	≥ 1	0	3	
Rescue analgesia	**Required**	4	5	0.7177
	Not required	26	25	

Table 2. Caudal block, residual motor block and rescue analgesia requirement of both the groups

	0min	15 min	30 min	45 min	60min	1.5h	2h
Group L	28(93.3%)	26(86.6%)	26	26	26	26	26
Group B	28	25(83.3%)	25	25	25	25	25

Table 3. Total no. of pain free patients in postoperative period (FLACC <4)

Discussion and conclusion

Day care surgery is a continually evolving specialty. This requires an anesthesia technique which has minimal stress response and maximum comfort with least residual effects to optimize early discharge. This has become easier with the advent of newer and safer anesthesia techniques and drugs.

Inguinal herniotomy is a commonly performed pediatric day care procedure. Caudal block is routinely used for herniotomy as it provides adequate intra-operative as well as post-operative analgesia. Though the caudal epidural block with local anesthetic provides excellent analgesia, residual motor blockade can cause discomfort. As children cannot express it out verbally, they become agitated and restless. This can be interpreted as lack of analgesia by parents and make them very anxious. Ideal caudal epidural block for ambulatory surgery should provide excellent, long duration analgesia with least residual motor blockade and minimum side effects. Bupivacaine introduced in 1963 has been the choice of local anesthetic drug used for caudal block since then.

Bupivacaine is a racemic mixture of R- and S- enantiomers, of which R- enantiomer is linked with the cardiotoxicity. [6] This led to the quest for search of longer acting drugs with a wide margin of safety. Hence the S-enantiomers were isolated, of which Levobupivacaine has been recently introduced in the Indian market. Introduction of S-enantiomers was a major breakthrough because the pharmacodynamics of these drugs were favorable to reduce the occurrence of cardiotoxicity, neurotoxicity [7,8] and unwanted motor blockade.

Literature scan revealed that there are no studies on the use of caudal levobupivacaine in the Indian pediatric population.

Levobupivacaine ([2S]-1-butyl-N-[2,6-dimethylphenyl] piperidine-2-carboxamide) is an amino-amide local anesthetic drug. The pKa of levobupivacaine is 8.1 which is similar to racemic Bupivacaine. It has a higher protein binding capacity (97%), resulting in less than 3% of free drug available in the circulation to cause inadvertent effects. [7]

Another S-enantiomer ropivacaine has also been exclusively researched in the pediatric and adult population through various routes for regional anesthesia. Relative analgesic potency of ropivacaine and levobupivacaine in caudal was assessed by Ingelmo et al and both were found to be equipotent from analgesic point of view. [9] Hence levobupivacaine can be substituted for bupivacaine and ropivacaine.

Ivani et al compared three different concentrations (0.125%, 0.2%, 0.25%) of levobupivacaine for caudal epidural in subumbilical surgeries using total volume of 1ml/kg. They found that 40% of the patients in the 0.25% group experienced motor blockade as compared to the 20% in the 0.2% group whereas none of the patients in 0.125% levobupivacaine group. [4] Though 0.125% was associated with less postoperative block it resulted in shorter duration of analgesia. Our experience with 0.25% bupivacaine for caudal epidural analgesia has been very promising. As both these drugs are stated to be equipotent we used similar concentration of both the drugs for caudal epidural analgesia.

Primarily we aimed to assess the caudal block efficacy and the block was equally effective in both the groups. Only one patient in levobupivacaine group had gross movements and 20%increase in the heart rate from the baseline resulting in ineffective caudal blockade. Locatelli B et al compared 0.25% bupivacaine, levobupivacaine and ropivacaine in a randomized, double blind phase 3 trial. They reported that levobupivacaine exhibited reliable analgesic efficacy which was comparable to bupivacaine and ropivacaine. [10] Levobupivacaine was found to be equally effective as bupivacaine and ropivacaine at similar concentrations for sub umbilical surgeries by Breschan et al and Ivani et al. [5,11]

Another primary aim was to study the residual motor blockade. Thirty percent patients in the levobupivacaine group versus seventy percent in the bupivacaine group had residual motor blockade (Modified Bromage$\geq$ 1) at

wake up (P = 0.004). Residual motor blockade gradually regressed and at 180 minutes post caudal epidural block 100% patients in the levobupivacaine had Modified Bromage of zero whereas 16.67% in the bupivacaine group still had Modified Bromage of ≥ 1 (P = 0.236).

Breschan et al compared analgesic efficacy and motor blockade of 1ml/kg of 0.2% levobupivacaine, ropivacaine and bupivacaine in 182 pediatric patients undergoing herniotomy and orchidopexy. During first hour postoperatively they reported that levobupivacaine and ropivacaine resulted in 25% and 10% motor blockade respectively which was significantly less (P<0.01) than that caused by bupivacaine (60% motor blockade).

They couldn't find any significant difference between the three groups after two hours. They suggested that due to its poor motor block, levobupivacaine can be preferred choice in day care procedure. [5]

Negri et al observed incidence of unwanted motor blockade as 21.4% with epidural infusion of 0.125% bupivacaine as compared to nil with levobupivacaine following hypospadias repair in children. [12]

A randomized phase III trial was conducted by Locatelli et al comparing 0.25% of either levobupivacaine, bupivacaine or ropivacaine in 99 pediatric patients undergoing sub umbilical surgeries.

They used total volume of 1ml/kg for orchidopexy or herniotomy and of 0.5ml/kg for phimosis or incision level below L_3. They found that at wake up only four patients in the bupivacaine group had modified bromage of zero versus sixteen patients each in levobupivacaine and ropivacaine group and the results were statistically significant (P<0.01).

Three hours after caudal, patients receiving levobupivacaine had significantly less motor blockade than patients receiving bupivacaine (P = 0.04). In post-hoc analysis, even after excluding patients receiving 0.5ml/kg of local anesthetics, bupivacaine was still found to produce significant motor blockade (P<0.01).

Our study results at wake up were parallel to those of Locatelli et al. [10]

Kaya et al conducted a prospective, randomized trial comparing 0.5ml/kg of 0.25% bupivacaine with similar dose of levobupivacaine in children undergoing circumcision surgery. They reported that 30% of patients in the bupivacaine group and 26.6% in the levobupivacaine group had Modified Bromage≥ 1 and at 150th minute the score was found to be zero in both the groups. [13] Frawley et al compared 1ml/kg of 0.25% levobupivacaine with similar dose bupivacaine in caudal blockade in 310 pediatric patients for lower abdominal surgery. They found that both the drugs exhibit similar analgesic efficacy and levobupivacaine is equally potent as bupivacaine. At 30 min following caudal anesthesia the incidence of motor blockade with racemic bupivacaine was 84% which decreased to 7% at 120 min. In the levobupivacaine group 85% experienced motor blockade at 30 min which decreases to 11% at 120 min and the difference was not statistically significant. [14]

Motor block potency of intrathecal amide local anesthetics was compared by Camorcia et al in parturient. They concluded that ropivacaine is the least potent whereas bupivacaine, the most potent and levobupivacine with intermediate potency to cause motor blockade. [15]

Epidural Levobupivacaine 0.5% resulted in less motor blockade compared to 50% enantiomeric excess Bupivacaine and racemic bupivacaine for abdominal hysterectomy in a study by Tanaka et al. Bromage score of two was noticed in 45% of patients in the levobupivacaine group versus 70% of patients in other two groups. [16]

We found satisfactory and comparable analgesia with both the drugs. More than 80% of the patients in both the groups remained pain free till the observation period. Our results were in concordance with other studies wherein the requirement of rescue analgesia was insignificant among the groups. [13]

Our study confirms that 0.75 ml/kg 0.25% levobupivacaine causes definitely less motor blockade compared to bupivacaine. This is the most commonly used volume and concentration of local anesthetic used for caudal

epidural analgesia for herniotomy. Although a moderate degree of residual blockade is not a major problem, inability to communicate the same in nonverbal children leads to agitation and excessive crying. This can become a cause of parental anxiety also. In addition to this it is always advisable to discharge a patient who is free of motor blockade in a day care setting.

To actually find out the significant difference with respect to the cardiotoxicity between the groups large number of subjects need to be recruited in the study.

To conclude levobupivacaine results in equally effective caudal block providing satisfactory perioperative analgesia comparative to bupivacaine with an additional advantage of less residual motor blockade. Levobupivacaine 0.25% 0.75ml/kg is a better choice compared to bupivacaine for caudal analgesia for herniotomy in children.

References

1. McClure JH. Ropivacaine. Br J Anaesth 1996;76:300-7.
2. Mcleod GA, Burke D. Levobupivacaine. Anaesthesia 2001;56:331-41
3. Santos AC, DeArmas PI. Systemic toxicity of levobupivacaine, bupivacaine and ropivacaine during continuous intravenous infusion to nonpregnant and pregnant ewes. Anesthesiology 2001;95:1256-64.
4. Ivani G, De Negri P, Lonnqvist PA, Eksborg S, Mossetti V, Grossetti R et al. Anesth Analg 2003;97:368-71.
5. Breschan C, Jost R, Krumpholz R, Schaumberger F, Stettner H, Marhofer P et al. A prospective study comparing the analgesic efficacy of levobupivacaine, ropivacaine and bupivacaine in pediatric patients undergoing caudal blockade. Paediatr Anaesth 2005;15:301-6.
6. Whiteside JB, Wildsmith JA. Developments in local anaesthetic drugs. Br J Anaesth 2001;87:27-35.
7. Bajwa SJ, Kaur J. Clinical profile of levobupivacaine in regional anaesthesia: A systematic review. J Anaesthesiol Clin Pharmacol 2013;29:530-9.
8. Casati A, Baciarello M. Enantiomeric local anaesthetics. Can ropivacaine and levobupivacaine improve our practice? Curr Drug Ther 2006;1:85-9.
9. Ingelmo P, Frawley G, Astuto M, Duffy C, Donath S, Disma N et al. Relative analgesic potencies of levobupivacaine and ropivacaine for caudal anaesthesia in children. Anesth Analg 2009;108:805-13.
10. Locatelli B, Ingelmo P, Sonzogni V, Zanella A, Gatti V, Spotti A et al. Randomised, double blind, Phase III, controlled trial comparing levobupivacaine 0.25%, ropivacaine 0.25% and bupivacaine 0.25% by caudal route in children. Br J Anaesth 2005;94:366-7.
11. Ivani G, Negri P, Lonnqvist P, Lerario M, Mossetti V, Difilippo A et al. Caudal anaesthesia for minor paediatric surgery: a prospective randomized comparison of ropivacaine 0.2% vs Levobupivacaine 0.2%. Paedaitr Anesth 2005;15:491-4.
12. Negri DE, Ivani G et al. A comparison of epidural bupivacaine, levobuivacaine and ropivacaine on postoperative analgesia and motor blockade. Anesth Analg 2004;99:45-8.
13. Kaya Z, Suren M, Arici S, Karaman S, Tapar H, Erdemir F. Prospective, randomized, double blinded comparison of effects of caudally administered levobupivacaine 0.25% and bupivacaine 0.25% on pain and motor blockade in children undergoing circumcision surgery. Eur Rev Med Pharmacol Sci 2012;16:2014-20.
14. Frawley G, Downie S, Huang G. Levobupivacaine caudal anaesthesia in children: A randomized double blind comparison with bupivacaine. Paediatr Anaesth 2006;16:754-60.
15. Camorcia M, Capogna G, Berritta C, Columb MO. The relative potencies for motor blockade after intrathecal ropivacaine, levobupivacaine and bupivacaine. Anesth Analg 2007;104:904-7.
16. Tanaka PP, Ogleari M, Valmorbida P, Tanaka MA. Levobupivacaine 0.5%, 50% enantiomeric excess bupivacaine and racemic bupivacaine in epidural

anaesthesia for lower abdominal procedures. Comparative study. Rev Bras Anestesiol 2005;55:597-605.