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Original Research Article

A Randomized Double Blind Controlled Study to Assess the Efficacy of Levobupivacaine Alone Versus Levobupivacaine with Ketamine in Subcutaneous Infiltration for Postoperative Analgesia in Lower Segment Cesarean Section

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Abstract

Aim: The aim of the present study to comparison of levobupivacaine alone versus levobupivacaine with ketamine in subcutaneous infiltration for postoperative analgesia in lower segment cesarean section.

Material and Methods: A randomized double blind controlled study conducted in the Department of Anaesthesiology, Patna Medical College and Hospital, Patna, Bihar, India for 1 year. A total of 30 parturients were randomly assigned to two groups (each with 15) based on computer-generated random numbers kept in sealed and numbered envelopes. Parturients in Group A received a subcutaneous surgical wound infiltration with a 0.5 percent levobupivacaine solution diluted with normal saline to a total of 32 ml at 2 mg/kg body weight to a maximum of 150 mg. Parturients in Group B received a subcutaneous surgical wound infiltration with a solution of 0.5 percent levobupivacaine 2 mg/kg body weight diluted with normal saline to a total volume of 32 ml, plus ketamine 1 mg/kg body weight diluted with normal saline to a total volume of 150 mg. The VAS scale and total analgesic use throughout the 24-hour postoperative period were used to assess the primary outcome, postoperative pain alleviation.

Results: The mean heart rates at zero hour (baseline) were comparable in groups A and B (P=0.871). Except at the 4th and 6th hour post-operative, the mean heart rate of group A was greater than that of group B, which was statistically insignificant at the majority of time periods.

Conclusion: In terms of greater pain relief, reduced need for rescue opioid analgesia, and no serious side effects, the study concluded that ketamine is a viable adjunct modality to levobupivacaine for local wound infiltration.

Keywords: Levobupivacaine, Multimodal Analgesia, N-Methyl-D-Aspartate Antagonist, Opioid Consumption, Subcutaneous Wound Infiltration.

Introduction

One of the most common concerns during and after caesarean procedures is postoperative pain.[1] Patients who have had a caesarean section have an additional compelling reason to be given adequate pain relief so that they can begin nursing and caring for their infant.

In addition, mobilization is a key factor in attenuating the risk posed by exaggerated thromboembolic phenomenon in pregnancy. [2,3]

Adequate post-operative analgesia in the obstetric patients is crucial as they have different surgical recovery needs which include breastfeeding and care of the newborn; these can be impaired if analgesia is unsatisfactory. The ideal post-CS analgesic regime should be efficacious without impacting the ability of mother to take care of the neonate and with minimal drug transfer through breast milk. However, observational data from developing as well as developed countries have shown that we are far from achieving these goals. In developing countries, limited availability of drugs, equipment and expertise are the major issues in providing adequate post-CS analgesia. [4,5]

As a result, post-operative discomfort should be managed as soon as feasible. Analgesia after surgery is an important element of perioperative management. Epidural analgesia, intravenous analgesia, and a patient-controlled analgesia pump are currently available for post-operative pain treatment.[6]

Levobupivacaine [(2S)1butylN(2, 6dimethylphenyl) piperidine2-carboxamide], an amino amide local anesthetic and the pure S (−) enantiomer of bupivacaine, has emerged as a safer alternative to other local anesthetic agents for regional anesthesia with less cardio toxicity and neurotoxicity among the commonly used local anesthetic agents.[7] Wound infiltration with levobupivacaine has a positive effect on wound healing due to its anti-inflammatory actions during the initial postoperative period and good postoperative analgesia following cesarean section.[8,9]

In a caesarean section, local anesthetic injection as an adjuvant to regional analgesia and general anesthesia is beneficial since it reduces opioid use. [10,11]

Levobupivacaine was recently launched into the Indian market and is now widely used in a variety of medical facilities. As a result of this growing use, evidence-based literature on risk and safety problems, as well as clinical difficulties connected to levobupivacaine, must be documented.[12] The purpose of this study was to compare the effects of levobupivacaine alone with levobupivacaine combined with ketamine in subcutaneous infiltration for postoperative analgesia in lower segment caesarean sections.[12]

Material and Methods:

A randomized double blind controlled study conducted in the Department of Anaesthesiology, Patna Medical College and Hospital, Patna, Bihar, India. for 1 year.

Methodology:

This study comprised 30 adult parturients who were Physical Status II or III according to the American Society of Anesthesiologists (ASA), had no medical or obstetrical concerns, and were scheduled for caesarean section under spinal anesthetic. The study excluded uncooperative, unwilling parturients, as well as those with a history of anaphylaxis to local anesthetics, opioids, and/or drugs to be used, current or previous history of drug abuse, psychiatric disease, body weight greater than 100 kg, and inability to understand the Visual Analog Scale (VAS).

Computer-generated random numbers kept in separate, sealed, and numbered envelopes were used to assign parturients to one of two groups (each with 15). Parturients in Group A received a subcutaneous surgical wound infiltration with a 0.5 percent levobupivacaine solution at 2 mg/kg body weight (rounded to nearest multiple of 10) to a maximum of 150 mg (maximum safe dose) diluted with normal saline to a total of 32 ml. Group B parturients received 0.5 percent levobupivacaine 2 mg/kg body weight (rounded to nearest multiple of 10) with ketamine 1 mg/kg body weight diluted with normal saline to a total volume of 32 ml as a subcutaneous surgical wound infiltration. The study drugs were prepared by an anesthesiologist who was not engaged in the anesthesia or postoperative management and handed over to the surgeon for subcutaneous infiltration prior to skin closure under strict aseptic conditions. Up to 24 hours following the surgical operation, a blinded observer assessed postoperative pain relief.

Before the surgery, a full preanesthetic checkup was performed, which included a detailed history, general physical examination, and systemic examination. Prior to surgery, routine examinations (full hemogram, coagulation profile, random blood sugar) and additional investigations were performed as needed. Preoperatively, the VAS was shown, and the scoring system was explained. The parturients were advised before to surgery that if they experience discomfort after surgery, they can seek an analgesic and that they can withdraw from the study at any moment.

After shifting the parturients to the operation theatre in left lateral position, prior to subarachnoid block, pulse rate (P.R), non-invasive blood pressure (NIBP), respiratory rate (R.R), oxygen saturation (SpO2), and electrocardiography (ECG) were recorded. These parameters were monitored throughout the procedure and recorded every 10 minutes. An intravenous access was achieved and preloading with 10 ml/kg body weight with balanced salt solution was done. Thereafter, subarachnoid block was given under full aseptic precautions in sitting position. A 26 Gauge Quincke's needle was introduced into the subarachnoid space at L3-4/L4-5 vertebral level. With the needle orifice cephalad and after confirmation of free flow of CSF, 2.0 ml of 0.5% heavy bupivacaine was injected through the spinal needle, which was withdrawn after the injection was given and the parturient was then turned supine. Surgery was allowed to proceed after sensory block was achieved up to level of T4 and motor block to level of modified bromage scale of 3. In case of partial/failed spinal anesthesia, general anesthesia was administered and the parturient was excluded from the study. At the end of surgery, parturients received subcutaneous skin infiltration of the study drug as per random group allocation in a blinded manner by the surgeon prior to skin closure.

Parturients were continuously monitored for heart rate, blood pressure, respiratory rate, and oxygen saturation. Postoperative pain scores and analgesic requirement were recorded along with hemodynamic parameters immediately after shifting to postoperative recovery room at 0 min, 30 minutes, 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours, respectively. Postoperatively, all parturients received slow infusion in 100 ml saline of diclofenac sodium 75 mg at 0 min and, thereafter, 8 hourly as part of multimodal postoperative analgesia regimen. Any parturient with VAS greater than or equal to 4 or at any point of time complained of pain was administered with 50 mg intravenous injection of tramadol, a rescue analgesic. Time of first rescue analgesic (FRA) request was noted. If the parturient still reported VAS ≥4 after 1 hour of receiving tramadol, similar doses

were repeated up to a maximum of 100 mg in contiguous 4 hours or 400 mg in 24 hours. The total rescue analgesic consumption for the 24 hours after surgery was recorded.

The observer (anesthesia resident posted in postanesthesia care unit) who recorded the postoperative vitals and analgesic consumption was blinded to the group allocation of the parturients to maintain the double-blind nature of the study. The outcomes of the parturients were evaluated in terms of quality of pain relief (as assessed by VAS score) and time of FRA administration, number of times rescue analgesic given, and the total consumption volume of analgesic 24 hours postoperatively. Parturients were also evaluated for any adverse effects. The primary outcome, postoperative pain relief was measured using the VAS scale and the total analgesic consumption during the 24 hours postoperative period. The secondary outcome, that is, patient satisfaction score (PSS) was assessed postoperatively at 24 hours and was subjectively graded as: Excellent (4), Good (3), Moderate (2), Poor (1).

Statistical Analysis:

Numbers and percentages were used to describe the data. The standard deviation and mean were calculated. The student t-test was used to compare quantitative variables. Chi square or exact tests were used to compare categorical data, as relevant. Statistical significance was considered as a probability value (P value) of less than 0.05. For all statistical calculations, SPSS version 20.0 was implemented.

Results:

In terms of demographic variables, we found that both groups were comparable. The mean heart rates at zero hour (baseline) were comparable in groups A and B (P = 0.871). Except at the 4th and 6th hour post-operative, the mean heart rate of group A was larger than that of group B, which was statistically insignificant at the majority of time periods.

Table 1 shows that in intra groups, the mean heart rate decreased gradually over time, but this was more pronounced in group B.

At all-time intervals, parturients in group A had higher mean VAS scores than those in group B, with statistically significant differences at 1, 4, 6, and 12 hours as indicated in table 2.

The mean time to FRA of group A was at 2.50 ± 1.12 hours (195 minutes) while that of group B was at 5.16 ± 2.88 hours (280 minutes). This difference was statistically significant (P=0.047). Thus, parturients in Group B complained of pain 1.8 hours later than the parturients in group A [Table 3].

Only 49.79 percent of parturients in group B who got ketamine as an adjuvant to levobupivacaine required rescue analgesia, whereas approximately 96.02 percent of parturients in group A who received levobupivacaine alone required rescue analgesia. [4th table]

In 24 hours, parturients in group A consumed 89.31 ± 57.75 mg of total opioids, compared to 63.35 ± 20.64 mg in group B. As a result, group A had a statistically significant higher opioid intake than group B (P = 0.001, Table 5).

6.67 percent of parturients in Group A had outstanding PSS, compared to 21.55 percent in Group B, while 20.98 percent of Parturients in Group A and 41 percent of Parturients in Group B had good PSS. As a result, the difference in patient satisfaction scores between the two groups was statistically significant (P = 0.007, table 6).

Table 1: Trends in postoperative mean heart rate

HR	Group A		Group B		*P*
	Mean	SD	Mean	SD	
0 h	90.79	14.31	90.21	10.81	0.871
30 min	90.32	14.21	90.72	12.74	0.721
1 h	92.52	16.35	89.72	13.51	0.421
2 h	94.50	15.91	87.82	11.80	0.051
4 h	94.22	15.88	86.80	11.21	0.030
6 h	93.36	13.82	86.61	9.57	0.021
8 h	86.75	12.80	87.87	9.72	0.612
12 h	84.82	11.12	85.22	9.93	0.932
16 h	83.43	11.67	83.32	7.82	0.930
20 h	83.90	11.83	83.82	8.33	0.919
24 h	84.21	9.93	82.87	8.87	0.421

Table 2: Mean VAS scores at various time intervals

VAS	Group A		Group B		P value
	Mean	SD	Mean	SD	
0 h	1.35	1.47	0.60	0.80	0.126
30 min	1.30	1.32	0.58	0.76	0.129
1 h	1.11	1.40	0.53	1.16	0.007
2 h	2.31	1.78	1.06	1.21	0.076
4 h	2.09	2.27	1.01	1.67	0.007
6 h	1.23	1.98	0.54	1.61	0.009
8 h	2.22	2.88	1.17	1.90	0.072
12 h	1.65	1.02	0.05	0.34	0.002
16 h	0.89	1.33	0.19	0.43	0.043
20 h	0.65	1.12	0.11	0.30	0.121
24 h	0.24	0.46	0.04	0.31	0.245

VAS – Visual analogue scale, $P<0.05$ significant

Table 3: Mean time to first rescue analgesia (FRA) and VAS at FRA

	Group A		Group B		P value
	Mean	SD	Mean	SD	
Time to first rescue analgesic consumption (h)	3.45	2.21	5.67	1.89	0.045
VAS AT FRA	3.78	1.09	4.21	0.78	0.432

Table 4: Total rescue analgesic consumption in 24 h (mg)

Total opioid analgesic consumption in 24 h (mg)	Group A		Group B		P value
	Mean	SD	Mean	SD	
	91.41	31.32	54.43	19.09	0.001

Table 5: Percentage of parturients requiring rescue analgesic in each group

	No	Yes
Group A	6.36	93.66
Group B	56.36	43.63

Table 6: Percentage of parturients with patient satisfaction score (PSS)

	Score 1	Score 2	Score 3	Score 4
Group A	11	57	24	6
Group B	0	30	41	19

Discussion:

Subcutaneous wound infiltration with local anesthetics is effective, safe, and low-cost, and it doesn't require any special skills. The analgesic efficacy of several local anesthetic wound infiltration strategies for postoperative analgesia following caesarean section was confirmed in a systematic study and metanalysis. With local anesthetic wound infiltration, they saw a statistically significant reduction in postoperative pain scores and overall opioid intake in just 24 hours. [13] We used levobupivacaine alone and levobupivacaine plus ketamine for local wound infiltration after cesarean section in view of their analgesic and anti-inflammatory properties along with a lesser cardio toxic profile.

Though we observed statistically significant prolonged times to FRA, the mean VAS score at FRA in both the groups was comparable— (4.23 ± 1.07) in group A and 4.21 ± 0.43 in group B). This implies that while levobupivacaine conferred profound analgesic effect in both the groups, addition of ketamine helped in prolonging the time required for FRA. Abdallah *et al*. evaluated the analgesic efficacy of preincisional infiltration with ketamine or levobupivacaine in 48 patients undergoing abdominal hysterectomy. They observed an increased duration of analgesia for up to 158 minutes with ketamine and 127 minutes with levobupivacaine (P = 0.001). The time to FRA in their study group usinglevobupivacaine was shorter compared to our study group A which can be attributed to the use of less volume and concentration of levobupivacaine solution for infiltration, that is, 20 ml and only 0.25% levobupivacaine in their study.[14]

Our study's total VAS ratings were higher in group A, with statistically significant higher values at 1, 4, 6, and 12 hours, which coincided with a statistically significant increase in heart rate in the same group at 4 and 6 hours. This means that the group infiltrated with levobupivacaine alone experienced larger initial peaks of pain, as evidenced by higher heart rates, at the same time of observations, whereas the group infiltrated with ketamine as an adjunct to levobupivacaine experienced less pain at the same time. As a result, adding ketamine to levobupivacaine improves its efficacy in terms of deep, long-lasting postoperative analgesia.

In group B, only 43.63 percent of the patients required rescue analgesia, but in group A, 93.66 percent required further tramadol supplementation. As a result, there was a statistically significant decrease in mean tramadol rescue analgesic consumption in group B, which was 63 mg compared to 96 mg in group A (P = 0.002). These data support ketamine's opioid sparing effect when combined with levobupivacaine, as well as a reduction in opioid-related side effects as nausea, vomiting, pruritus, and drowsiness. Demiraran et al. looked at 90 patients who had a caesarean section under general anesthesia and had 20 mL of 0.25 percent levobupivacaine injected into the wound at the end of the procedure. They found that the trial group consumed 483 mg of tramadol while the placebo group consumed 560 mg (P = 0.07). The study group's overall higher tramadol intake than group A can be related to the study group's use of a lower concentration and volume

of levobupivacaine. Furthermore, we used multimodal analgesia by giving all parturients an intravenous injection of diclofenac 75mg every 8 hours, which was not part of their trial. [15]

A Cochrane review encompassing 20 studies on parturients who received wound infiltration following cesarean section under regional anesthesia observed a statistically significant decrease in morphine consumption at 24 hours compared to placebo. However, this analysis revealed no additional advantage in terms of patient satisfaction score upon addition of ketamine to continuous wound infiltration with 0.125% bupivacaine, where the catheter was placed above the fascia affecting the spread of drug.[16] On the contrary, we found that group B had a statistically and clinically significant improvement in patient satisfaction compared to group A (P = 0.02), which can be attributed to the use of a higher concentration of levobupivacaine with ketamine, 0.5 percent.

Conclusion:

In terms of greater pain relief, reduced need for rescue opioid analgesia, and no serious side effects, we concluded that ketamine is a viable adjunct modality to levobupivacaine for local wound infiltration.

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