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Original Research Article

EFFICACY OF SUBCUTANEOUS LEVOBUPIVACAINE VERSUS LEVOBUPIVACAINE–TRAMADOL INFILTRATION FOR POSTOPERATIVE ANALGESIA IN ELECTIVE CAESAREAN SECTION: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND STUDY IN A TRIBAL DISTRICT TERTIARY CARE CENTRE OF CENTRAL INDIA

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ABSTRACT

Background: The present study aimed to assess the effectiveness of wound infiltration with levobupivacaine combined with tramadol in reducing postoperative pain and minimizing the need for additional analgesics during the immediate postoperative period in parturients undergoing elective caesarean section

Materials and Methods: Seventy-four pregnant women aged 18–40 years scheduled for elective caesarean section under spinal anaesthesia were enrolled after Institutional Ethics Committee approval. Participants were randomly assigned into two equal groups. Group A received 20 mL of 0.25% levobupivacaine, while Group B received 75 mg tramadol added to 20 mL of 0.25% levobupivacaine. Postoperative analgesia was evaluated by recording the time to first analgesic request, Visual Analog Scale (VAS) scores, and total consumption of diclofenac and tramadol over 24 hours.

Results: Group B exhibited lower VAS scores at most time points compared to group A, indicating prolonged analgesic effect in Group B. At15 minutes, 16th hr and 24th hr the mean VAS score was significantly lower in the combination group (0.16 ± 0.37), (0.35± 0.63), (0.19 ± 0.52) compared to the Levobupivacaine alone group (0.73 ± 1.41), (1.27 ± 1.52), (0.95 ± 1.05) with a p-value of 0.0225, 0.0014, and 0.0003 respectively, suggesting a statistically significant difference in early and late pain relief. Postoperative analgesic assessment revealed that patients in Group B (Levobupivacaine + Tramadol) experienced a significantly longer duration before requesting the first analgesic (380 ± 230 min) compared to Group A (Levobupivacaine alone; 190 ± 130 min), indicating superior and prolonged analgesia with the addition of tramadol (p = 0.0002). Additionally, total diclofenac consumption over 24 hours was significantly lower in Group B (112 ± 36 mg) than in Group A (138 ± 32 mg), reflecting reduced requirement for supplemental analgesics (p = 0.006). Adverse effects were comparable in two groups.

Conclusion: Wound infiltration with a combination of tramadol and levobupivacaine appears to provide effective postoperative analgesia in patients undergoing caesarean section under spinal anaesthesia, and may be considered a useful analgesic option.

Keywords: Levobupivacaine, Tramadol, Postoperative analgesia, Infiltration.

INTRODUCTION

Single-shot spinal anaesthesia is the most frequently used technique for elective caesarean sections, providing reliable intraoperative anesthesia.[1] However, patients often experience moderate to severe pain in the postoperative period, making effective analgesia essential. Multimodal pain management strategies have gained attention, with local wound infiltration emerging as a simple, safe, and effective component. This technique has been shown to reduce opioid consumption, minimize complications, shorten hospital stays, and lower healthcare costs, particularly in settings with limited access to opioids, patient-controlled analgesia devices, or infusion pumps.[2]

Among local anaesthetics, levobupivacaine has demonstrated efficacy across various surgical procedures, including local infiltration, with analgesic effects lasting between 4 and 24 hours.[3,4] Tramadol, a synthetic opioid analogue, exerts its analgesic action through both weak μ-opioid receptor agonism and modulation of monoaminergic pathways, and it has been shown to inhibit peripheral nerve transmission.[5] When combined with local anaesthetics, tramadol can enhance analgesic efficacy, potentially by modulating sodium channels or through effects similar to clonidine.[6]

The present study aims to evaluate whether wound infiltration with levobupivacaine and tramadol can reduce postoperative pain and decrease the need for additional analgesics in women undergoing caesarean delivery under spinal anaesthesia.

MATERIALS AND METHODS

This prospective, randomized, double-blind, controlled study was conducted at a tertiary care teaching hospital Government Medical College, Gondia, Maharashtra after obtaining approval from the Institutional Ethics Committee (GMC/GONDIA/PHARMACOLOGY/IEC/07/2023). The study period extended from August 2023 to December 2024. All procedures adhered to the principles of the Declaration of Helsinki (1975, revised 2024) and Good Clinical Practice (GCP) guidelines. Patient safety and well-being were prioritized throughout the study

A total of 74 parturients undergoing elective caesarean sections under spinal anaesthesia were enrolled. The sample size was calculated assuming the expected mean and standard deviation of the time to first rescue analgesic consumption in the levobupivacaine group as σ1 (3.29, 2) as per the previous study by Paridhi Kaler et al.[7] Assuming the minimum clinically important difference in the levobupivacaine–tramadol group as 1.51 hours. Other parameters considered for sample size calculation included 80% power of study and 5% two-sided alpha error.

A total of 74 patients were enrolled. Formula used for sample size calculation:

$$N = \frac{(u + v)^2(\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$$

N = sample size

σ1, σ0 = Standard deviations (σ1 = 2 and σ0 = 2.5)

u = Two-sided percentage point of the normal distribution corresponding to 100% - the power = 80%, u = 0.84

v = Percentage point of the normal distribution corresponding to the (two-sided) significance level for significance level = 5%, v = 1.960

The required sample size as per the above-mentioned calculation was 35 in each group. To account for a non-participation rate / loss to follow-up rate of about 5%, another 2 subjects were added to the sample size in each group. Hence the final required sample size was 37 subjects in each group.

A total of 74 parturients, aged 18–40 years, scheduled for elective caesarean section with Pfannenstiel incision under spinal anaesthesia, were enrolled. Exclusion criteria were: patient refusal, uncontrolled systemic disease, contraindications to spinal anaesthesia, known drug allergy, Patients with current or past history of drug abuse, patients with body weight > 100 kg, failure of spinal block, conversion to general anaesthesia, or who have psychiatric, neuromuscular, or cardiovascular disease or impairment of hepatic or renal function.

In this double-blinded randomized controlled trial both the study subjects and the assessor of VAS score were blinded. An anaesthetist not involved in the conduct of anaesthesia & postoperative management prepared the drugs and handed them over to the obstetrician for subcutaneous infiltration prior to skin closure under all aseptic precautions. The blinded observer assessed the postoperative pain relief up to 24 hours after the subcutaneous infiltration of the allotted drug.

Patients were enrolled in the study after a thorough preanesthetic check-up and routine investigations which included a complete hemogram, coagulation profile, and random blood sugar. VAS score was explained and shown to all the patients preoperatively and they were informed that they can request for analgesics at any time after surgery if they feel pain.

After shifting the parturient to the operation theatre, baseline heart rate, respiratory rate, mean arterial blood pressure, and SPO_2 were recorded. An intravenous access was secured with 20 gauge IV cannula and preloading was done with 10 ml/kg body weight of ringer lactate over 20 minutes. Intravenous injection ondansetron 4 mg and injection metoclopramide 10 mg were given. Thereafter, subarachnoid block under all aseptic precautions was given in sitting position with 25G spinal needle at L3–L4 / L4–L5 intervertebral space after confirmation of free clear flow of CSF.

Injection bupivacaine 0.5% (heavy) 2.0 ml was injected through spinal needle, then patients were turned supine slowly within 5 seconds. The surgery was allowed to start when sensory block achieved up to T6 level and Bromage motor block grade 3.In case of partial / failed spinal anaesthesia, general anaesthesia was administered and patient was excluded from the study.

Hypotension (MAP < 20% from baseline), bradycardia (< 60 bpm), nausea and vomiting due to spinal anaesthesia were managed as per standard guidelines in all patients. (Rescue dose of IV injection ondansetron 1 mg for vomiting, IV injection mephentermine 6 mg bolus for hypotension, inj atropine 0.6mg iv for bradycardia).Patients were monitored for heart rate, respiratory rate, mean arterial blood pressure, and SPO_2 every 3 minutes for first 15 minutes, then every 5 minutes till the closure of uterus and rectus sheath.

After the closure of uterine muscle layers and rectus sheath, subcutaneous infiltration of study drug as per random group allocation in blinded manner was given by the operating surgeon.

Randomization and Intervention:

Patients were randomly allocated to one of the two groups (Group A and Group B) according to computer-generated random numbers kept in separate sealed & numbered envelopes.

- **Group A:** received 20 ml local subcutaneous wound infiltration with levobupivacaine 0.25% (not exceeding the toxic dose)
- **Group B:** received subcutaneous wound infiltration with levobupivacaine 0.25% and tramadol 75 mg (dose not exceeding 1.5 mg/kg) to a total volume of 20 ml

The time of subcutaneous infiltration of test drug was taken as zero minute. Observation started from this zero minute onwards. Patients were continuously monitored for VAS score, first dose of rescue analgesia, number of times rescue analgesia was needed, and vitals monitoring (heart rate, respiratory rate, MAP, SPO_2) for the first hour every 15 minutes**,** then at 2, 4, 8, 12, 16, 20 and 24 hours after subcutaneous infiltration.

All parturients received injection Diclofenac 75 mg in 100 ml N**S** over 20 minutes every 8 hourly as part of multimodal postoperative analgesia. If any patient complained of pain or VAS > 4, then IV Tramadol 1mg/kg was given over 5 minutes, and this time was noted as first dose of rescue analgesia. VAS was reassessed after 10 minutes. If VAS > 4 or patient complained of pain, again IV Tramadol 1mg/kg was given.

Total dose of Tramadol was not to exceed 100 mg in 6 hours.

The time of first rescue analgesia**,** number of doses**,** and total Tramadol consumption were recorded.

Patients were evaluated for the following adverse effects:

- Nausea with or without vomiting
- Hypotension (MAP < 20% of baseline)
- Respiratory depression (RR < 10/min)
- Bradycardia (HR < 60/min)
- Rash, redness, or signs of inflammation at the infiltration site

Primary Endpoint: Duration of postoperative analgesic effect (VAS Score)

Secondary Endpoints: Total analgesic consumption in 24 hours and incidence of adverse effects (nausea, vomiting, local reactions).

Statistical methods

Data were analysed using IBM SPSS Statistics (IBM Corp., USA) for Windows, Version 20.0. Data are presented as number (%) or mean ± SD as appropriate. Quantitative data were compared using one-way analysis of variance. Qualitative variables were compared using Fisher's exact test. A P value < 0.05 was considered significant.

RESULTS

Seventy four parturients were enrolled in study and all of them have completed study. Baseline demographic characteristics, including age, height, weight, and BMI, were comparable between Group A (levobupivacaine alone) and Group B (levobupivacaine with tramadol), with no statistically significant differences observed (P > 0.05). [Table 1]

Table 1: Baseline characteristics of women allocated to both groups during elective Caesarean delivery

Parameter	Group A (Levobupivacaine alone) Mean± SD	Group B (Levobupivacaine + Tramadol) Mean± SD	P value
Age in years	23.76 ± 4.26	23.0 ± 4.26	**1.0**
Height (cm)	143.72 ± 7.08	144.08 ± 6.73	**0.99**
Weight(kg)	**54.08 ± 4.66**	**54.16± 4.36**	**0.96**
BMI	26.26 ± 2.32	24.14 ± 2.066	**0.97**

Data are presented as mean ± standard deviation (SD). P values were calculated using the independent t-test. BMI: Body Mass Index.

Table 2: VAS values at different time intervals

Time point	Group A (Levobupivacaine alone) Mean± SD	GroupB (Levobupivacaine + Tramadol) Mean± SD	P value
15 min	0.73 ± 1.41	0.16 ± 0.37	0.0225

2 hour	1.0 ± 1.43	0.62 ± 0.76	0.1616
4 hour	1.05 ± 1.84	0.73 ± 0.8	0.3307
8 hour	0.78 ± 1.36	0.89 ± 1.43	0.7396
12 hour	0.78 ± 1.2	0.51 ± 0.99	0.2954
16 hour	1.27 ± 1.52	0.35 ± 0.63	0.0014
20 hour	0.35 ± 0.89	0.78 ± 1.23	0.0874
24 hour	0.95 ± 1.05	0.19 ± 0.52	0.0003

Values are presented as mean ± standard deviation (SD). Pain scores were measured using the Visual Analog Scale (VAS). P values were calculated using the independent t-test. Statistically significant differences are considered at $P < 0.05$.

Group B exhibited lower VAS scores at most time points, indicating prolonged analgesic effect in Group B. At 15 minutes, 16th hr and 24th hr the mean VAS score was significantly lower in the combination group (0.16 ± 0.37), (0.35± 0.63), (0.19 ± 0.52) compared to the Levobupivacaine alone group (0.73 ± 1.41), (1.27 ± 1.52), (0.95 ± 1.05) with a p-value of 0.0225, 0.0014, and 0.0003 respectively, suggesting a statistically significant difference in early and late pain relief. [Table 2]

Table 3: 24-Hour Postoperative Analgesic and Antiemetic Use and Time to First Analgesia

Parameter	**Group A (Levobupivacaine alone) Mean± SD**	**Group B (Levobupivacaine + Tramadol) Mean± SD**	**P-value**
Time to first analgesic request (min)	190 ± 130	380 ± 230	0.0002*
Total diclofenac consumption (mg)	138 ± 32	112 ± 36	0.006*
Metoclopramide consumption (mg)	11.0 ± 3.5	10.5 ± 2.5	0.398

Values are presented as mean ± SD for continuous variables. Patient satisfaction scores are presented as the number of patients. *p < 0.05 indicates statistical significance.

Postoperative analgesic assessment revealed that patients in Group B (Levobupivacaine + Tramadol) experienced a significantly longer duration before requesting the first analgesic (380 ± 230 min) compared to Group A (Levobupivacaine alone; 190 ± 130 min), indicating superior and prolonged analgesia with the addition of tramadol (p = 0.0002). Additionally, total diclofenac consumption over 24 hours was significantly lower in Group B (112 ± 36 mg) than in Group A (138 ± 32 mg), reflecting reduced requirement for supplemental analgesics (p = 0.006). Metoclopramide consumption was comparable between the groups (Group B: 10.5 ± 2.5 mg; Group A: 11.0 ± 3.5 mg; p = 0.398), suggesting no difference in postoperative nausea and vomiting. Overall, the combination of levobupivacaine with tramadol provided more effective and longer-lasting postoperative pain control without increasing antiemetic requirements. [Table 3]

Table 4: Adverse Effects Frequency

Time Point	**Group**	**Nausea**	**Vomiting**	**Local Site Reaction**
15 min	A B	0 1	0 1	0 0
2 hour	A B	0 0	0 0	0 0
4 hour	A B	0 0	0 0	0 0
8 hour	A B	0 0	0 0	0 0
12 hour	A B	0 0	0 0	0 0
16 hour	A B	0 0	0 0	0 0
20 hour	A B	0 0	0 0	0 0
24 hour	A B	0 0	0 0	0 0

Values represent the frequency (number of patients) of adverse effects observed at each time point. No statistical comparison was performed due to the low incidence of events.

The assessment of adverse effects revealed that Group A did not exhibit any complications such as nausea, vomiting, or local site reactions at any observed time point. In contrast, Group B showed minimal adverse effects, with isolated cases of nausea and vomiting reported in the early postoperative period (15 and 30 minutes), which resolved thereafter. No local site reactions were observed in either group throughout the study duration. Overall, both groups demonstrated a

favourable safety profile, with only transient and minimal adverse effects noted in Group B. [Table 4]

DISCUSSION

Effective perioperative pain management is essential for patients undergoing caesarean section, as it ensures comfort, minimizes side effects, and provides continued analgesia beyond the recovery room. Adequate postoperative pain control is a key factor in determining when a patient can be safely discharged from the recovery area. While opioids are highly effective for managing severe pain, their use is often limited due to the risk of adverse effects. In contrast, local anaesthetic agents can offer effective pain relief while avoiding many of the complications associated with opioid therapy.

Hence wound infiltration along with systemic non-steroidal anti-inflammatory drugs appears to be an attractive alternative to manage pain.

Our study found that tramadol offers more prolonged postoperative analgesia than levobupivacaine alone, with a reduced need for additional pain medication. In caesarean section patients, providing effective postoperative pain relief and enabling early mobilization are crucial. The chosen analgesic technique should be dependable, efficient, and associated with minimal side effects. For these reasons, wound infiltration is commonly employed as a simple and effective method for postoperative analgesia.

Although studies have shown that wound infiltration with local anaesthetics provides effective postoperative analgesia, these drugs must be used cautiously because of potential cardiovascular and central nervous system toxicity. Most toxic reactions during wound infiltration occur due to inadvertent intravascular injection. To minimize these risks, levobupivacaine is often preferred over bupivacaine, as it has a lower potential for cardiotoxicity and neurotoxicity.[8]

Tramadol, which has a low risk of cardiovascular toxicity, has been shown to possess peripheral local anaesthetic properties. Experimental studies have demonstrated that direct application of tramadol to nerves can produce a local anaesthetic effect. For example, Tsai et al. observed this effect when tramadol was applied to the sciatic nerve in rats,[9] while Pang et al. reported that intradermal tramadol produces analgesic effects comparable to those of lidocaine.[10] In clinical studies, Altunkaya et al. compared tramadol and lidocaine as subcutaneous local anaesthetics in patients undergoing minor surgical procedures. They found that tramadol not only provided effective local anaesthesia but also reduced postoperative analgesic consumption and prolonged the duration of analgesia, suggesting that tramadol can be a valuable alternative to conventional local anaesthetics in minor surgeries.[11]

Further, wound infiltration with local anaesthetics has been reported to lower interleukin-10 levels while increasing substance P at the surgical site. Additionally, local anaesthetics administered subcutaneously have been shown to possess both bacteriostatic and bactericidal properties.[12,13]

Local anaesthetic infiltration and abdominal nerve blocks, when used alongside regional or general anaesthesia, have been shown to reduce opioid consumption in caesarean section patients. The use of nonsteroidal anti-inflammatory drugs as adjuncts can provide additional analgesic benefits.[14] Preoperative skin infiltration with 0.5% bupivacaine has been reported to decrease postoperative pain,[15] while ropivacaine infiltration and peritoneal spraying as preemptive analgesia have been found to reduce the need for narcotics and other analgesics, as well as lessen severe pain immediately after caesarean delivery under general anesthesia.[16] Clinical studies have also demonstrated the efficacy of levobupivacaine in a variety of surgical procedures, including local infiltration, with a reported duration of action ranging from 4 to 24 hours.[3,4,17]

In the study by Demiran et al, wound infiltration with tramadol or levobupivacaine significantly reduced postoperative pain following caesarean section compared to placebo. Patients receiving tramadol infiltration had the lowest 24-hour opioid consumption, while levobupivacaine also provided meaningful analgesic benefits. Early postoperative pain scores were lower in both treatment groups, indicating effective immediate pain control. Although there was no significant difference in the need for supplemental diclofenac, the results suggest that tramadol and levobupivacaine infiltration are effective, safe, and practical techniques for reducing postoperative pain and opioid requirements in caesarean section patients under general anesthesia.[18]

Our study demonstrated that wound infiltration with tramadol in combination with levobupivacaine provides superior postoperative analgesia compared to levobupivacaine alone in caesarean section patients. The addition of tramadol significantly prolonged the time to first analgesic request (380 ± 230 min vs. 190 ± 130 min; $p = 0.0002$) and reduced total 24-hour diclofenac consumption (112 ± 36 mg vs. 138 ± 32 mg; $p = 0.006$), indicating more sustained pain relief and lower supplemental analgesic requirements. Early postoperative pain scores were also lower in the tramadol group, while metoclopramide use was similar between groups, suggesting comparable rates of nausea and vomiting. These findings support that tramadol combined with levobupivacaine is a safe, effective, and practical approach for postoperative analgesia following caesarean section.

No allergic, cardiovascular, or central nervous system complications were observed in patients receiving levobupivacaine or tramadol wound

infiltration. To our knowledge, there is limited data on the optimal dosing of levobupivacaine and tramadol for wound infiltration in caesarean delivery under spinal anaesthesia, and our findings may provide guidance for clinical practice or future studies.

Despite the promising findings, this study has several limitations. The sample size was relatively small, which may limit the generalizability of the results. Additionally, the study was conducted at a single centre, and variations in surgical technique, patient demographics, or perioperative care could influence outcomes. Only the first 24 hours postoperatively were assessed, so longer-term pain control and recovery parameters were not evaluated. Patient-reported pain scores are inherently subjective and may be influenced by individual pain tolerance.

Another important limitation is the potential neurotoxicity of wound infiltration with tramadol. Although clinical studies report effective analgesia and favourable outcomes with tramadol infiltration and peripheral nerve blocks, there is limited preclinical safety data. Some animal studies have suggested that tramadol may cause neuronal toxicity, highlighting the need for caution.[9,19] Further preclinical and clinical studies are required to establish the safety and optimal dosing of tramadol for wound infiltration.

CONCLUSION

In conclusion, wound infiltration with tramadol or levobupivacaine significantly prolonged postoperative analgesia and reduced the need for additional analgesics. This technique appears to be a safe, effective, and practical option for postoperative pain management in caesarean section patients.

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