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Comparison of bupivacaine infiltration with and without tramadol for post-operative analgesia in split skin graft donor sites: A prospective randomized controlled study

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ABSTRACT

Background: Split skin graft (SSG) creates a new partial-thickness wound at the donor site. Donor site pain is the most common concern in the post-operative period. Local infiltration of the donor site is an effective way to reduce immediate post-operative pain. Prolonged pain relief is always sought after. **Aims and Objectives:** In this study, we intend to know if the addition of tramadol to bupivacaine local infiltration prolongs post-operative analgesia. **Materials and Methods:** Sixty patients posted for SSG with donor site in the thigh were included in the study. They were divided into Group BB, who received local infiltration of the donor site with 0.25% bupivacaine, and Group BT who received local infiltration with 0.25% bupivacaine and 50 mg tramadol. Visual analog scale (VAS) score up to 24 h, time of 1st rescue analgesia, total analgesic consumption in 24 h, and side effects were noted. **Results:** Patients in Group BB had significantly higher VAS scores at 8, 9, 10, 11,12, and 16 h as compared to Group BT. The time of first rescue analgesia was higher in Group BT with 721.03 ± 54.79 min as compared to Group BT which had 463.21 ± 43.89 min and these values were statistically significant. Total rescue analgesia consumption was significantly higher in Group BB with 2928.57 ± 377.96 g when compared with Group BT which had 2068 ± 257.88 g. There were no significant side effects. **Conclusion**: Local infiltration of the donor site with bupivacaine and tramadol combination decreased the post-operative pain score, total analgesic consumption, and prolonged the time of first rescue analgesia as compared to local infiltration of donor site with bupivacaine alone with minimum side effects.

Key words: Bupivacaine; Donor site; Infiltration; Tramadol; Split skin graft; Post-operative analgesia

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INTRODUCTION

Partial thickness skin grafting is a commonly performed procedure for skin defects and post-burns involving the upper limb. General anesthesia is used to harvest the skin graft from the ipsilateral or contralateral thigh to cover the defect. Harvesting a split-thickness skin graft creates a new partial-thickness wound referred to as the donor site. The donor site is much more painful post-operatively than the recipient site.[1] Donor site pain is a common complication in the early post-operative period.[2] This pain needs to be alleviated for reduction of post-operative morbidity and speedy recovery of the donor site.[3]

Inadequately managed pain after surgery can negatively affect the well-being of the patient at multiple levels, causing hypertension, myocardial ischemia, arrhythmias, poor wound healing, and prolonged hospitalization.[4]

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Opioids are used to manage post-operative pain but they come with side effects such as respiratory depression, sedation, dizziness, and ileus in the post-operative period prolonging the hospital stay.[5,6]

Various methods are used to alleviate the pain in the donor site. They include subcutaneous infiltration with local anesthetic after harvesting the graft[7] applying topical agent such as EMLA cream[8] 45 min before harvesting the graft, ice application, and hydrocolloid- and polyurethane-based wound dressings[9]. Furthermore, opioids or non-opioid analgesics are given in the early post-operative period to relieve the pain from the donor site. EMLA cream has a limited duration of action of 1–2 h only. Furthermore, ice application and specialized wound dressings also act only for a limited period.

As a significant part of surgical pain originates from the surgical site, it is logical to use local anesthetics at the site of the wound to manage post-operative pain.[10] Various advantages have been described for subcutaneous administration of drugs, which include avoiding first-pass metabolism, improved patient comfort, and good analgesia[11] The wound site infiltration with bupivacaine has a bacteriostatic and bactericidal effect that reduces the risk of infection at the wound site[12] (20) and also, it has immediate post-operative analgesia, even though it has a limited analgesia time of 5–8 h, subcutaneous infiltration of local anesthetic in the donor site has proved to be effective for reducing early post-operative pain. However, since the duration of local anesthetic is limited, certain adjuvants are often added to local anesthetic such as fentanyl, dexamethasone[1] clonidine, and dexmedetomidine to prolong the duration of post-operative analgesia. Tramadol, a synthetic opioid, is unique owing to its low propensity to cause respiratory depression, pruritis, and tolerance. It is easily available owing to it lying outside the realm of narcotic drugs and psychotropic substances act.[13]

Tramadol has been successively used intravenously in the post-operative period as an analgesic. It is also used as an adjuvant to 0.5% bupivacaine intrathecally to prolong the duration of spinal anaesthesia.[14] There are some studies where it is effectively used as an adjuvant to local anesthetic in brachial plexus block[11,15,16] or wound infiltration after cesarean section.

However, studies evaluating the combined effect of bupivacaine and tramadol on skin grafting donor site pain are scarce. This research is designed to study the effect of the addition of tramadol as an adjuvant to 0.25% bupivacaine for subcutaneous infiltration of the donor site after harvesting the split skin graft (SSG) in relieving post-operative pain.

Aims and objectives

To study the effect of addition of tramadol as an adjuvant to 0.25% bupivacaine for subcutaneous infiltration of donor site after harvesting the split skin graft (SSG) in relieving post-operative pain.

MATERIALS AND METHODS

The study was designed as a prospective randomized controlled trial. The inclusion criteria were adult patients aged 18–60 years, requiring a split-thickness skin grafting for reconstruction of the upper limb wound defect wherein the donor site area involving only one thigh. We excluded patients with American Society of Anesthesiologists (ASA) more than grade II, those with lower limb neuropathies, allergies to local anesthetics or tramadol, and those patients who needed more than 100 square cm of SSG or the duration of surgery was more than 90 min.

Groups:

- Group BB: Infiltration of the donor site with 0.25% bupivacaine 19 mL+1 mL NS
- Group BT: Infiltration of the donor site with 0.25% bupivacaine 19 mL+1 mL (50 mg) Tramadol.

Methods

After institutional ethical committee approval, patients participating in the study according to inclusion criteria were included in the study. Proper pre-anesthetic evaluation was done for all patients included in the study. Written informed consent was taken. The procedure was explained to the patients and they were familiarized about the post-operative pain score: Visual analog scale (VAS).

The patients were categorized into two groups. Group BB received infiltration of the donor site with 0.25% bupivacaine 19 mL+1 mL NS before harvesting the graft. Moreover, Group BT received infiltration of the donor site with 0.25% bupivacaine 19 mL+1 mL (50 mg) tramadol. The randomization was done by computer-generated random numbers and allocation happened by sealed envelopes blinding the principal investigator in the following way.

When the patient entered the pre-operative room, the nurse in charge of the pre-operative room looked up the computer-generated random number charts and kept a closed sealed envelope indicating the group allocated in the patient's case sheet.

As the patient enters the operation theater, the junior resident who was not involved in the study opened the sealed envelope and the nursing staff who had washed for the case loaded the drug according to the group allocated.

The anesthesiologist connected the monitors according to ASA standards, ECG, pulse oximetry, and non-invasive blood pressure (NIBP) monitor. Basal vitals such as heart rate (HR), NIBP, and oxygen saturation (SpO_2) were noted. 1-pint Ringer lactate was started in an 18 G intravenous (IV) cannula on the dorsum of the opposite hand. All patients received general anesthesia with endotracheal intubation. Patients were given an injection of glycopyrrolate 0.2 mg IV, an injection of midazolam 1 mg IV, an injection of fentanyl 2 mcg/kg IV, induced with an injection of propofol 2 mg/kg IV, and an injection of vecuronium 0.1 mg/kg IV to facilitate intubation. Controlled mechanical ventilation was given and anesthesia was maintained with O_2: N_2O:2: 2, 1% sevoflurane and intermittent doses of vecuronium 1 mg. Vitals line HR, NIBP, and SpO_2 were monitored at the start of surgery and then every 15 min, till the surgery was over.

The operating surgeon harvested the split-thickness skin graft using a Watson modification of Humby's knife from the anterolateral aspect of the thigh adjusted to 0.2 mm thickness. Hemostatis was provided by dressing with wet gauze for 15 min. Subcutaneous infiltration of the donor area was done with a mixture of 20 mL of local anesthetic solution which was prepared by the scrub nurse. It was done after the graft harvesting to avoid edema or hematoma to the graft itself. The injection was through transverse lines 2 cm apart by 26 G, one and half inch needle.

Outcomes were measured in terms of the donor site pain measured at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, and 24 h using the VAS score. Whenever the VAS score was more than 4, rescue analgesia was given with an injection of paracetamol 1 g IV, and the time of first rescue analgesia was noted. Total rescue analgesia consumed within 24 h was noted. No side effects were noted.

Sample size calculation

Based on a survey of previous literature for an outcome variable on mean score severity pain score in two groups comparison with the minimum difference of 0.90 and standard deviation 1.5 at 18th h of assessment to attain significance at type I error (α error) of at least 5%, Type II error(β error) at 10%, and keeping statistical power above 90%, the sample size of 60 (30+30) was adequate for two group assessment clinical study after adjusting for lost-to-follow-up, drop-out rates, and withdrawals for consent.

RESULTS

Sixty patients were found eligible and were included in the study. There were 30 patients in each group. In 2 patients, the duration of surgery exceeded 90 min and in 1 patient, the required graft was more than 100 cm^2, so these 3 patients were excluded from the analysis. Hence, a total of 57 patients were analyzed. There was no statistical difference between Group BB and Group BT regarding age, sex, weight, body mass index, ASA grading, and duration of surgery (Table 1).

Patients in Group BB had significantly higher VAS scores at 8, 9, 10, 11, 12, and 16 h as compared to Group BT (Figure 1). The time of first rescue analgesia was higher in Group BT with 721.03±54.79 min as compared to Group BT which had 463.21±43.89 min (Figure 2) and these values were statistically significant. Total rescue analgesia consumption was higher in Group BB with 2928.57±377.96 g when compared with Group BT which had 2068±257.88 g (Table 2).

Three patients in Group BB and 5 patients in Group BT had nausea and 1 patient in Group BB and 2 patients in Group BT had vomiting episodes (Table 3). These patients were treated with an injection of ondansetron 4 mg IV. None of our patients had symptoms of local anesthesia toxicity.

DISCUSSION

Donor site pain is the most common complication seen in the early post-operative period, which is considered to be the major cause of morbidity leading to delay in discharge from the hospital. In this study, we used local anesthetic bupivacaine infiltration in the donor site for post-operative pain relief. We compared this with adding tramadol as an adjuvant to bupivacaine and found that by adding tramadol as an adjunct to bupivacaine for local infiltration gave better post-operative pain relief as compared to bupivacaine alone. Local bupivacaine infiltration works by delivering the anesthetic directly to the surgical site, where it blocks nerve conduction and reduces pain perception in the immediate area.[5]

In our study, we observed that the time of demand for the

Table 1: Patient demographic profile and duration of surgery

Parameter	Group B	Group BT	P-value
Age (in years)	39.07±12.14	42.03±10.86	0.335
Sex (M/F)	13/15	11/18	
Weight (kg)	67.82±4.95	65.34±8.78	0.197
Height (cm)	156.29±2.95	157.03±3.16	0.360
Body mass index (kg/m²)	62.48±7.61	63.51±8.14	0.058
ASA grading (I/II)	12/15	16/11	
Duration of surgery (min)	74.11±9.43	71.03±5.73	0.141

Group B: Group bupivacaine, Group BT: Group bupivacaine+50 mg tramadol. ASA: American Society of Anesthesiologists

Table 2: Comparison of study variables of patients in two groups

Variables	Group B	Group BT	Total	P-value
Time of 1st rescue analgesia (min)	463.21±43.89	721.03±54.79	594.39±139.07	<0.001**
Total paracetamol consumed in 24 h (g)	2928.57±377.96	2068.97±257.88	2491.23±538.61	<0.001**

Group B: Group bupivacaine, Group BT: Group bupivacaine+tramadol. **Statistically highly significant

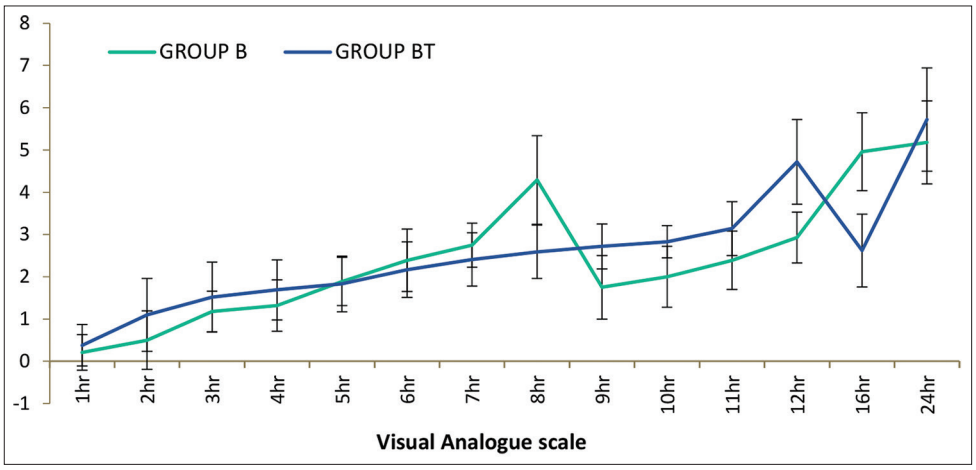

Figure 1: Visual analog scale

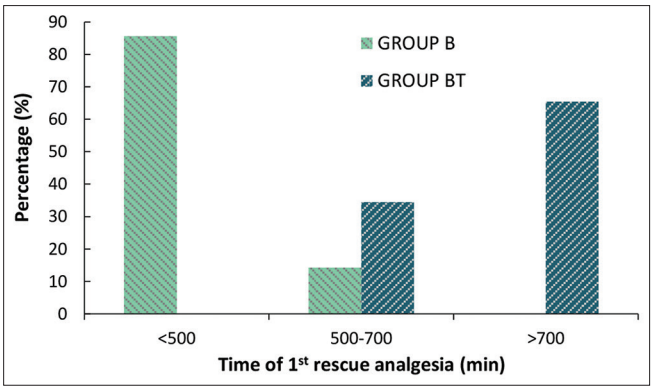

Figure 2: Time of first rescue analgesia

first rescue analgesia was 721.03±54.79 min in Group BB as compared to Group BT which had 463.21±43.89 min. The time of first rescue analgesia was higher in our study, as the tramadol 50 mg which is used as an adjunct to local anesthetics had prolonged the duration of post-operative analgesia. Similar to our study, Emadi et al.[16] in their study compared bupivacaine, tramadol, and bupivacine–tramadol combination for infiltration in the surgical incision for lower segment cesarean section and concluded that the pain score in the combination group was less than the bupivacaine group, and the bupivacaine group was less than the tramadol group over time, and the use of bupivacaine and tramadol combination can provide more acceptable effects in controlling the pain after surgery.[16]

Similar to our study, Tsegaye Demeke Gebremedhin et al. used local wound infiltration with a mixture of tramadol and bupivacaine versus bupivacaine alone in those undergoing lower abdominal surgery and observed that local wound infiltration with bupivacaine–tramadol decreases the postoperative pain score, total analgesic consumption, and has a prolonged time to first analgesia request as compared to bupivacaine alone. The possible reasons for the mechanisms of action supporting the rationale for using tramadol as an adjunct with local anesthetics are: First, the presence of serotonin (5-hydroxytryptamine, 5-HT) subtype 3 (5-HT3) receptors on peripheral nerve endings and in the dorsal laminae of the spinal cord indicate possible peripheral sites of analgesic action for tramadol.[17] Second, tramadol has local anesthetic properties, possibly by blocking K+channels.[17] Finally, tramadol's monoaminergic actions include agonism at peripheral a2 receptors, suggesting a role in nerve blocks similar to that of clonidine.[10,18]

Wound infiltration with bupivacaine has been shown to reduce the levels of interleukin 10 and increase substance P in the wound.[19]

In our study, the VAS score was higher in Group BB at 8th h and the VAS score was higher in Group BT at the 12th and 24 h in Group BT. Similar to our study, Emadi et al.,[16] and Roopa Sachidananda[11] et al. in their study also observed lower VAS scores in Group where tramadol was added to bupivacaine.

In our study, we found a significant increase in the rescue analgesic consumption of paracetamol in bupivacaine

Table 3: Side effects-frequency distribution of patients in two groups

Variables	Group B (%)	Group BT (%)	Total (%)	P-value
Nausea				
No	25 (89.3)	24 (82.8)	49 (86)	0.705
Yes	3 (10.7)	5 (17.2)	8 (14)	
Vomiting				
No	27 (96.4)	27 (93.1)	54 (94.7)	1.000
Yes	1 (3.6)	2 (6.9)	3 (5.3)	
Local anesthesia toxicity				
No	28 (100)	29 (100)	57 (100)	1.000
Yes	0 (0)	0 (0)	0 (0)	
Total	28 (100)	29 (100)	57 (100)	

Chi-square test/Fisher exact test

group. Roopa Sachidananda et al.[11] compared cesarean wound infiltration with bupivacaine alone and bupivacine–tramadol combination and concluded post-operative analgesia was longer in tramadol–bupivacaine group and rescue analgesia – diclofenac consumption was higher in bupivacaine group. Their results were similar to our study where the time of first rescue analgesia was longer and rescue analgesia used in our study, paracetamol consumption in 24 h was lower in tramadol–bupivacaine group.

In our study, we observed that side effects such as nausea and vomiting were not statistically significant between the groups. None of our patients had local anesthesia toxicity. JOACC[18] et al. in their study found that tramadol wound infiltration resulted in insignificant plasma levels (0.02–0.09 ng/mL), which was much lower than the therapeutic level (100–300 ng/mL), indicating possible local effects of tramadol.[8] This might also be the reason for the significantly less incidence of unpleasant side effects such as post-operative nausea and vomiting, which is observed after IV tramadol. Similar to our study, Emadi et al.,[16] had no cases of local anesthesia toxicity.

Limitations of the study

However, there were certain limitations in our study. We did not calculate the plasma levels of bupivacaine and tramadol after local wound infiltration.

We considered the surgeries which had a duration <90 min only and also the donor site <100 cm^2. This has to be studied in larger donor site area >100 cm^2, and duration >90 min with larger sample size, to validate the study in larger population.

CONCLUSION

Local infiltration of the donor site is an effective method of post-operative pain, as it reduces the IV analgesic consumption and the related side effects. Local infiltration of the donor site with bupivacaine and tramadol combination decreased the post-operative pain score, and total analgesic consumption and prolonged the time of first rescue analgesia as compared to local infiltration of the donor site with only bupivacaine. Subcutaneous infiltration of the donor site with a combination of bupivacaine and tramadol can be used for post-operative analgesia after SSG with better and prolonged.

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Authors' Contributions:
KP- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **AS-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; design of study, statistical analysis and interpretation; literature survey and preparation of figures.

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