Original Article

Comparative efficacy of ropivacaine and levobupivacaine in combined femoral and lateral femoral cutaneous nerve block with adjuvant magnesium for post-operative analgesia

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ABSTRACT

Background and Aims: Patients with burns may require multiple surgeries, but poor general condition and underlying protein energy malnutrition make them unsuitable candidates for general or spinal anaesthesia. This study evaluated the role of magnesium sulphate as an adjuvant with levobupivacaine and ropivacaine used in combined femoral and lateral femoral cutaneous nerve (LFCN) blocks in burn patients with relative sparing of thigh portion. **Methods:** This prospective, randomised, double-blind study included 54 adult patients of 18–65 years age, undergoing split-thickness skin graft harvest from the thigh, allotted to three equal groups of 18 each. Group L patients received femoral nerve (FN) block with 15 mL of 0.5% levobupivacaine and 8 mL for LFCN block; Group LM patients received 14 mL of 0.5% levobupivacaine along with 1.0 mL of 15% magnesium sulphate for FN block, 7.5 mL of 0.5% levobupivacaine with 0.5 mL of 15% of magnesium sulphate to LFCN block and Group R patients received 15 mL of 0.5% ropivacaine for FN block and 8 mL of 0.5% ropivacaine for LFCN block. Time to block onset and complete surgical block, duration of analgesia, total analgesic dose and the overall analgesia satisfaction score were measured in the first 24 h post-operatively. Quantitative data were analysed with ANOVA and qualitative data subjected to Chi-square tests. Intergroup comparison was performed with independent *t*-test. **Results:** The duration of post-operative analgesia did not differ with the addition of magnesium ($P = 0.610$). Time to onset of the block was significantly decreased with the addition of magnesium ($P = 0.0341$), but time to complete surgical block onset was similar across the groups. **Conclusion:** Both ropivacaine and levobupivacaine have good perioperative analgesic efficacy. Magnesium as an analgesia adjuvant with levobupivacaine does not prolong the duration of post-operative analgesia.

Key words: Femoral nerve block, lateral femoral cutaneous nerve block, levobupivacaine, magnesium sulphate, ropivacaine

INTRODUCTION

In split skin grafting, donor site pain is severe and prolonged compared to grafted site.[1] Regional nerve blocks efficaciously provide primary anaesthesia and prolonged post-operative analgesia. For lower-limb skin grafts, a combined femoral nerve (FN) and lateral femoral cutaneous nerve (LFCN) regional block can anaesthetise the broad anterolateral thigh surface for graft harvesting. Levobupivacaine and

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ropivacaine, the newer pure single S-(-)-enantiomers of bupivacaine—manifest improved cardiovascular and central nervous system safety profiles.[2,3]

Burn patients often require multiple skin reconstructive surgeries, with prolonged hospital stay and chronic inflammatory state potentially contributing to hypoalbuminaemia and protein energy malnutrition. Hypoalbuminaemia predisposes to drug toxicity, even with normal doses, especially for local anaesthetics (LA) with high affinity for protein binding.[4] Published literature, predominantly western studies, recommend approximately 30 mL (150 mg) or more LA dosing for FN/combined FN and LFCN block.[5,6] In the Indian clinical scenario, and especially in patients with chronic burn wounds, the average body mass index is low or on the lower limit of normal range; a direct application of the recommended dosages may be inappropriate. A safe adjuvant may decrease LA drug dose. Recent reports indicate magnesium sulphate to have promising analgesic effects in peripheral nerve blocks (PNBs).[4,7-9] Therefore, this study was undertaken to evaluate the efficacy of magnesium sulphate in PNB with duration of post-operative analgesia as a primary objective.

METHODS

This prospective, double-blind, randomised study included 54 patients between age of 18 and 65 years of either gender with chronic burn wounds who underwent tertiary intention wound closure requiring <4% total body surface area (TBSA) skin graft between November 2012 and January 2014 at our institution after obtaining institutional review board approval. Coagulopathy, infection over potential anaesthetic injection site, pregnancy and lactation were exclusion criteria.

Standard monitoring protocols, establishing intravenous (IV) access and recording baseline parameters were followed pre-operatively. Midazolam 0.05 mg/kg IV was administered as premedication 10 min pre-procedure. A computer-generated randomisation schedule facilitated patient disposition into three equal groups (n = 18 per group). Group L patients received FN block with 15 mL of 0.5% levobupivacaine and 8 mL for LFCN block; Group LM patients received 14 mL of 0.5% levobupivacaine along with 1.0 mL of 15% magnesium sulphate for FN block, 7.5 mL of 0.5% levobupivacaine plus 0.5 mL of 15% of magnesium sulphate to block LFCN; and Group R patients received 15 mL of 0.5% ropivacaine for FN block and 8 mL of 0.5% ropivacaine for LFCN block. Study drugs were constituted by an independent investigator, who refrained from further study participation. All blocks were administered by the same experienced anaesthesiologist (who had completed at least ten successful FN and LFCN blocks), supervised by a senior anaesthesiologist, and both were blinded to study drug. Overly anxious patients were administered IV fentanyl 25 μg (maximum 1 μg/kg) before beginning of procedure. Patients complaining of paraesthesia before graft harvesting were administered 'ketofol' (equal concentrations of ketamine and propofol in the same syringe) as a single dose of 0.3–0.5 mg/kg IV, 1 min before proceeding with graft harvest.

With the patient supine, anatomical landmarks of the FN and LFCN were sought at the inguinal crease 1 cm lateral to the pulsations of the femoral artery and 2 cm medial and inferior to the anterior superior iliac spine, respectively, marked and infiltrated with 0.5 mL 1% lignocaine subcutaneously. A 21 gauge, 50 mm, short-beveled, Teflon-coated, unipolar needle (Stimuplex™), with peripheral nerve stimulator was used, in coordination with quadriceps femoris contractions for clearly visible to and fro patellar movement at current <0.5 mA for FN block. With negative aspiration, a 1 mL test LA dose was administered and loss of muscle twitches checked. The full LA dose was injected gradually. A blunt-tipped needle perpendicularly inserted into skin for the LFCN (purely sensory nerve), popped through tensor fasciae lata, and current applied gradually from 1 to 0.5 mA to check for tingling along lateral thigh and persistent paraesthesia. Tingling at currents <0.3 mA indicated an intraneural placement and needle was withdrawn slightly before LA injection. In cases without paraesthesia, LA was injected in a fan-shaped manner between fasciae latae and lateral border of sartorius, after confirming negative aspiration.

Sensory and motor block evaluation was repeated at 5-min intervals for 30 min after block, with the former evaluated by loss of pinprick sensation (22 gauge hypodermic needle) along FN–LFCN distribution over anterolateral thigh. Motor block (a complete surgical blockade) for FN was defined as inability to move the foot in the blocked limb.

Pain assessment at 1, 2, 4, 6, 12 and 24 h post-operatively using a visual analogue scale (VAS; score 0–10 cm)

was rated with 0 representing no pain and 10, worst pain imaginable. Diclofenac 75 mg (IV, administered over 5 min) was used as rescue analgesic if VAS score was >3. For persistent pain 30 min after diclofenac, IV tramadol 1 mg/kg (with ondansetron 0.15 mg/kg) was used as additional drug, with no analgesic repeated within next 6 h. At pain assessment, patients who were asleep were assigned a score of ≤3.

Parameters assessed included time to surgical blockade (time from the end of anaesthetic injection to complete loss of pin-prick sensation in LFCN/FN innervation area/inability to move ankle and foot), duration of post-operative analgesia, determined by time to first demand for rescue analgesic post-operatively; VAS score at 1,2, 4,6,12 and 24 h, and on the first demand of rescue analgesic and whenever supplemental analgesics were administered; total analgesic (diclofenac and tramadol) doses in the first 24 h post-operatively; time to onset of nerve block (sensation in the affected limb <30% [0% = no sensation, 100% = normal sensation] vs. contralateral leg);[10] Side effects and complications (e.g., nausea, vomiting, constipation,paraesthesia, drowsiness, blurred vision, hearing trouble, dysgeusia or fatigue) were assessed. Satisfaction score was scored as 3,2 and 1 corresponding to excellent, good and poor quality, respectively.

For statistical significance, with a power of 80% and a level of significance of 5%, a study population of at least 17 patients per group was needed to evaluate >1-h difference in demand of analgesia among groups. Quantitative data analysis was done by ANOVA, whereas qualitative variables were subjected to Chi-square tests. Intergroup data comparisons were analysed with an independent *t*-test. All data were presented as mean ± standard deviation (SD). $P < 0.05$ was considered statistically significant.

RESULTS

Of the 54 patients included, two were excluded (one for refusal of surgery under PNB and the other for a graft area >4%, detected late). No significant between-group differences existed with regard to demographics [Table 1] or total duration of surgery. The success rate with FN block was nearly 100%, but there were two failed cases with the LFCN block. For FN and LFCN blocks, mean block onset times (±SD) were 4.18 (±1.13) and 5.46 (±1.56) min in Group LM, significantly shorter ($P = 0.03405$ and $P = 0.011$) than in Groups R (5.53 ± 1.91 and 7.40 ± 2.67 min) and Group L (5.11 ± 1.37 and 7.20 ± 1.78 min), respectively. Differences in time to complete surgical block were statistically insignificant for both FN and LFCN blocks [Table 2].

Eighteen patients did not require supplemental analgesia (44% of Group L, 22% of Group R and 33% of Group LM). The maximum frequency of analgesia demand, two times in the 24-h duration, was seen with 11.11%, 22.22% and 5.56% of patients in Groups L, R and LM, respectively; the rest availed a single dose of diclofenac. Of 18 patients in Group L, 16 in Group R, and 18 in Group LM, 8, 4 and 6 patients did not require post-operative analgesia, respectively. The remaining patients consumed mean dose of 82.50 mg, 100 mg and 75 mg of diclofenac per patient for Groups L, R and LM respectively, without significant between-group differences [$P = 0.91556$; Table 2]. No patient required tramadol supplementation. The mean VAS scores at 0, 1, 2, 4, 6, 12 and 24 h [Figure 1] remained between 2 and 2.5 and no significant difference was noted among groups. Meantime (±SD) for first rescue analgesic demand differed significantly [Table 2] ($P = 0.0025$; 1286 [±190], 1101 [±208] and 1316 [±150] min in Groups L, R and LM, respectively), with Group R having statistically significant differences

Table 1: Baseline patient characteristics by study group

Demographic parameter	Group L	Group R	Group LM
n	18	18	18
Sex distribution (male: female)	66.67:33.33	77.22:27.78	61.11:38.89
Age (years), mean±SD	35.89±13.35	35.17±18.10	32.33±14.32
Height (cm), mean±SD	164.69±7.30	164.67±7.05	168.89±5.04
Weight (kg), mean±SD	51.89±11.26	55.56±12.52	58.67±13.31
BMI, mean±SD	19.04±3.08	20.46±4.18	20.47±3.98

P<0.05 – Significant; *P*<0.001 – Highly significant. Group L – Levobupivacaine; Group R – Ropivacaine; Group LM – Levobupivacaine plus magnesium; BMI – Body mass index; SD – Standard deviation

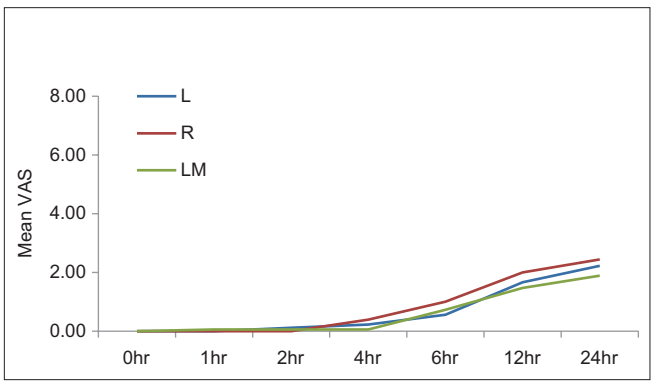

Figure 1: Post-operative analgesia assessed by visual analogue scale score for pain (L: Levobupivacaine; R: Ropivacaine; LM: Levobupivacaine plus magnesium)

Table 2: Assessment of analgesia efficacy over 24 h among study groups

Group	Mean±SD		TOSB FN (min)	Mean±SD				
	TOB FN (min)	TOB LFCN block (min)		TOSB LFCN (min)	Time to first diclofenac dosing (min)	Total diclofenac per group (mg)	VAS at diclofenac administration	Analgesia satisfaction score
L	5.11±1.37	7.20±1.78	19.33±2.17	21.40±2.47	1286±190	825±23.70	4.50±0.53	2.39±0.61
R	5.53±1.91	7.40±2.67	18.24±3.23	20.27±2.46	1101±208	1200±27.22	4.36±0.63	2.33±0.59
LM	4.18±1.13	5.46±1.56	19.59±3.55	19.50±3.71	1316±150	900±22.60	4.18±0.40	2.28±0.57
P	0.03405	0.011	0.493	0.12	0.002521*	0.91556	0.41052	0.977052

*Highly significant *P*<0.01; L – Levobupivacaine; R – Ropivacaine; LM – Levobupivacaine plus magnesium; TOB – Time of onset of block; TOSB – Time of onset of complete surgical block; FN – Femoral nerve; LFCN – Lateral femoral cutaneous nerve; SD – Standard deviation; VAS – Visual analogue scale

versus Groups L and LM (*P* value 0.003 and 0.004, respectively).

Intraoperative sedation as supplement was not needed in 23 patients (44.23%); 29 (55.77%) subjects required supplementation with fentanyl and or ketofol. Eleven (20.73%) patients experienced pain during graft harvesting; ketofol (0.2–0.5 mg/kg) was administered before continuing with graft harvest [Table 3]. Overall satisfaction score for post-operative analgesia was comparable among groups ($P = 0.97$), with average satisfaction score >2. No features of LA toxicity were observed in any patient; however, one subject in Group L and 3 in Group LM complained of pruritus.

DISCUSSION

A combined FN and LFCN block provides wider surface analgesia, with added advantages of a regional block. To achieve adequate post-operative analgesia with PNB, sufficient LA volume is required to effectively block a large segment of the nerve; however, the excess volume has a risk of systemic absorption and related toxicity. With ultrasound (US) guidance, precise PNB can be achieved. One study reported the effective volume for an FN block to be ~22 mL,[6] approximately 50% lower dose than with conventional method.[5,9-11] This study[6] tested 0.5% ropivacaine 15 mL (75 mg) and 8 mL (40 mg) for FN and LFCN blocks, respectively, and ropivacaine provided the shortest duration of post-operative analgesia (18.35 ± 3.48 h).

Adjuvant magnesium did not prolong post-operative analgesia in our study. Ambiguity exists in the published literature on the reported role of magnesium in PNB, with studies in animal models demonstrating an adjuvant role of magnesium in PNB[12] and subsequent human studies also reporting a similar advantages in femoral, interscalene, epidural and brachial plexus blocks.[8,9,11] However, more recently, studies in animals have not supported these claims, probably because magnesium acts by blocking N-methyl-D-aspartate receptors deficient at peripheral nerve sites.[13] Our results are in concordance with these recent studies, with no significant difference in prolongation of post-operative analgesia evident in the adjuvant magnesium study group. Another study by Hung *et al*. in a rat model demonstrated that magnesium co-administered with LA reduced the duration of nerve block.[14]

Time of onset of sensory block was lesser with adjuvant magnesium. Two studies of interscalene block[11] and combined FN and interscalene block[15] did not observe similar results, but other studies of epidural anaesthesia[8] and FN block[9] reported early block onset with magnesium. The surface charge theory indicates magnesium carries a cationic charge that neutralizes negative surface charge on the external neural membrane, making the cell surface hyperpolarised and difficult to stimulate,[16] which possibly explains earlier onset of nerve block; however, this mechanism might potentially reduce the number of open or activated Na channels where LA acts, thereby depotentiating the LA effect.[17] Although no adverse effects of magnesium use were observed here, a few reports indicate magnesium enhances the excitability threshold in Aβ fibres more than in pain carrying C fibres.[13] Karasawa *et al*.[18] reported a selective effect of magnesium on myelinated motor fibres but not in pain signal-transmitting nerve fibres, causing motor paralysis but incomplete analgesia.

Here, levobupivacaine provided better post-operative analgesia compared to ropivacaine. The relative potency of the LAs via intrathecal route in labour anaesthesia is reported to be approximately1:0.9:0.7, i.e., bupivacaine >levobupivacaine >ropivacaine.[19] However, this difference may not be significant if their pure base, rather than salt, is taken into consideration. Concentration of levobupivacaine in base form (i.e., 0.5%) translates to an equipotent dose in its salt form (0.56%). Because other LAs are supplied in salt form, this difference (13%) becomes significant.[20] Studies

Table 3: Intraoperative supplementation of fentanyl and/or ketofol

Groups	*n* (%)			
	L	R	LM	Total
None	7 (38.88)	6 (33.33)	10 (55.55)	23 (42.59)
Fentanyl (1 μg/kg)	9 (50.00)	7 (41.17)	7 (41.17)	23 (44.23)
Ketofol* (0.2-0.5 mg/kg)	4 (22.22)	5 (29.41)	2 (11.76)	11 (20.37)
Fentanyl and ketofol	2 (11.11)	2 (11.11)	1 (5.55)	5 (9.25)

*Ketofol – Equal concentration of ketamine and propofol in same syringe. L – Levobupivacaine; R – Ropivacaine; LM – Levobupivacaine

using levobupivacaine, bupivacaine and ropivacaine in axillary brachial plexus block, combined interscalene block and femoral block and sciatic nerve block have demonstrated similar efficacy.[5,15] Another US-guided study of popliteal nerve block demonstrated that sensory block lasted 24 h post-operatively with ropivacaine and levobupivacaine.[21]

We infer that a combined FN and LFCN block is inadequate for primary anaesthesia, and a combination of sedation and PNB analgesia is preferable. Fentanyl, in doses not exceeding 1 μg/kg, and ketofol (i.e., ketamine and propofol in the same syringe) in small aliquots of 0.2–0.5 mg/kg provide short-duration sedation with analgesia without respiratory compromise. Our study results demonstrated that levobupivacaine has better efficacy compared to ropivacaine; however, this claim may need a re-look if their pure base form is taken into consideration. In market, levobupivacaine is supplied in base form whereas ropivacaine in salt form. Magnesium as an adjuvant does not enhance post-operative analgesia with levobupivacaine. Although mean block onset time was slightly shortened with magnesium, time to complete surgical block did not differ significantly among the groups.

Patients with burns may face difficulty in obtaining clearance for general or spinal anaesthesia for multiple surgeries, probably due to large TBSA involvement, difficult airway management, position-related problems or associated comorbidities. In patients in whom general or spinal anaesthesia is unsuitable, an FN block with or without an LFCN block together with light sedation can provide both primary anaesthesia as well as prolonged post-operative analgesia.

Our study has limitations. With study duration limited to 24 h, we could not report on subjects demonstrating post-operative analgesia that lasted longer than 24 h; therefore, we cannot conclusively comment on individual drug efficacy, and a more comprehensive and longer duration study would be required to evaluate these aspects. The significant difference achieved with regard to total duration of analgesia was not corroborated by the quantitative consumption of analgesic, with further studies in a larger population potentially facilitating validation of these findings. Use of a nerve stimulator together with a blind approach was inadequate for comparing successful analgesia between FN and LFCN blocks, and US guidance may help overcome this gap. Our study results are applicable to single-shot FN, and LFCN blocks, with caution recommended in the extrapolation of these results to other PNB or continuous catheter techniques. The minimal side effects observed in our study are not sufficient to justify conclusions on individual drug safety, and further study in a large patient population will be required to establish the safety profiles of these LA in these blocks.

CONCLUSION

Levobupivacaine and ropivacaine (0.5%) can provide satisfactory post-operative analgesia in patients undergoing split-thickness skin graft harvest from the anterolateral thigh under FN block and/or LFCN block. The addition of magnesium sulphate does not prolong post-operative analgesia duration. For primary anaesthesia, a combined FN and LFCN block alone is inadequate and may necessitate supplementary measures for effective anaesthesia.

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Conflicts of interest

There are no conflicts of interest.

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