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Comparison of bupivacaine versus bupivacaine-dexamethasone infiltration for postoperative analgesia in skin graft donor sites: a randomized trial

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Abstract

Background: Skin grafting, both partial and complete thickness, is frequently used in reconstruction of traumatic soft tissue defects. It is of great value not only for functional and anesthetic purposes in the field of plastic surgery, but also for other surgical specialties.

Of all the problems in the early postoperative period, pain is considered the most important, ameliorating it can lead to significant reduction in postoperative morbidity and faster recovery of the skin donor site.

Objective: To evaluate use of dexamethasone as adjuvant for bupivacaine in subcutaneous local anesthesia infiltration for skin graft donor sites, on quality of pain relief and total dose of analgesic requirements in the early hours postoperatively.

Methods: Ninety-five patients were randomly allocated to receive local bupivacaine infiltration (group LB) (48 patients), or dexamethasone plus bupivacaine (group LB + D) (47 patients) in skin donor site after skin harvesting. In addition to basic demographic data, patients were compared for numerical rating scale (NRS), total dose of morphine including morphine equivalents, time to 1st breakthrough pain (over an observational period during the first 12 h postoperatively) and duration of surgery.

Results: Numerical rating scale figures were significantly better ($P < 0.05$) in group (LB + D) than group (LB) in the first 7 h postoperatively. Likewise, consumption of morphine or its equivalents was considerably less, as well as time to first breakthrough pain. Duration of surgery was not significantly different between both groups.

Conclusion: Addition of dexamethasone to bupivacaine provided effective analgesia for patients undergoing skin grafting surgery, with less need for rescue analgesia in the early postoperative period to bupivacaine alone.

Keywords: Donor site, Skin graft, Breakthrough pain, Rescue analgesia, Bupivacaine

Introduction

Plastic surgery is a technically demanding field; reconstruction of tissue defects requires great attention to achieve anesthetic and functional recovery. Skin grafting is the most-often applied procedure to reconstruct areas of various sizes and anatomical locations. Nevertheless,

complications are inevitable for these types of procedures (Akan et al. 2003).

The postoperative management of the partial-thickness raw area involves several strategies (Henderson et al. 2012).

These techniques carry the potential risk for adverse events such as excessive pain, scarring, fluid loss, delayed wound healing, immobilization, and hyperpigmentation (Akan et al. 2003).

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Donor-site pain is the foremost alarming complication within the early postoperative period. If split thickness skin graft donor site is much painful postoperatively than the recipient site, then good graft take is probably going (Moriarity Sign) (Oluwatosin et al. 2000).

Alleviation of this pain is able to do considerable reduction in postoperative morbidity and quick recovery of the donor site (Akan et al. 2003).

Local anesthetics are widely used to provide postoperative analgesia, despite this there is always a problem in maintaining a satisfactory level of pain relief beyond 4–8 h postoperatively after skin infiltration with the longest-acting local anesthetic agents (bupivacaine, levobupivacaine, and ropivacaine) (Oluwatosin et al. 2000).

Attempts to prolong the impact of local anesthetic blockade by increase in doses or by development of new medications have been unsuccessful, principally attributable to toxicity.

Prolonged infusions of local anesthetics via indwelling catheters have been useful, especially when applied at peripheral nerve sites or within the epidural space, but are unsuitable at other sites. Several pharmaceutical agents have also been tried as adjuvants to local anesthetics to lengthen the analgesic effect (Holte et al. 2002).

A more enticing theory holds that dexamethasone increases the activity of inhibitory potassium channels on nociceptive C-fibers (via glucocorticoid receptors), thus decreasing their activity (Abdallah et al. 2015).

Why dexamethasone would prolong regional anesthesia could be a subject of a lot of discussion. One such mechanism is that steroids cause a degree of vasoconstriction, thereby acting by decreasing local anesthetic absorption (Rawal 2008).

We thus sought to determine the effect of dexamethasone, as an adjuvant for bupivacaine, on the quality and duration of analgesia from local infiltration of bupivacaine for skin graft donor site surgeries.

Materials and methods

Ethics

This randomized controlled study was approved by Ain Shams University Research Ethics Committee (REC) (FMASU R75/2018) written informed consent was obtained from all the patients.

Sample size determination

Using STATA program, setting alpha error at 5% and power at 90%, result from previous study by Bhattacharjee et al. 2014 showed that pain score at 8th hour for group I was 3.84 ± 1.02 compared to 3.25 ± 0.76 for group II. (Bhattacharjee et al. 2014) Based on these findings the required minimal sample size was 47 cases for each group.

Patients

The study was performed at Ain Shams University Hospitals, Egypt, from October 2018 to February 2019. The inclusion criteria for the study included patients' age group from 18–75 years of either sex, American Society of Anesthesiologists Physical Status classification I–II and scheduled for split thickness skin grafting to cover full thickness skin burn or degloving injury after trauma. The exclusion criteria were inability to cooperate, immunosuppressive therapy, body mass index $> 35 \text{ kg/m}^2$, diabetes, lower-limb neuropathy, daily intake of glucocorticoids or opioids, patients who need area of coverage more than 10 cm^2 , allergy to any drug used in the study, alcohol, or drug abuse.

Randomization and blinding

The patients included in the study were randomly allocated to 1 of 2 parallel groups: (1) bupivacaine only (LB) group ($n = 48$): received 20 ml bupivacaine 0.5% + 20 ml normal saline. (2) bupivacaine plus dexamethasone (LB + D) group ($n = 47$): received 20 ml bupivacaine 0.5% + 18 ml normal saline + 8 mg dexamethasone 2 ml. A random allocation sequence was generated electronically using online randomization service from <https://www.random.org>. The project medicine was prepared by two independent assistants not involved in other parts of the study. All persons involved were blinded to the randomized allocation.

Anesthesia

Patients were monitored with Continuous 5 Lead Electrocardiography, noninvasive blood pressure measurement, capnography, and pulse oximetry. The patients received general anesthesia with IV induction by propofol 2 mg/kg, fentanyl 1 mcg/kg, and atracurium 0.5 mg/kg was used to facilitate intubation. Controlled mechanical ventilation was initiated utilizing a tidal volume of 7 ml/kg and respiratory rate finely adjusted to maintain an end-tidal carbon dioxide value of 30–35 mmHg. Anesthesia was maintained by sevoflurane inhalational anesthesia. After completion of the operation, muscle relaxant was reversed by neostigmine 0.05 mg/kg + atropine 0.02 mg/kg.

Study interventions

Split thickness graft harvesting was performed by three plastic surgeons. The grafts were harvested from the posterolateral aspect of the thigh using a powered dermatome (Acculan Dermatome, Aesculap Power Systems, Aesculap Inc., USA) adjusted to 0.2 mm thickness. The hemostasis was provided by dressing in wet gauze for 15 min before the actual dressing, after the patient took general anesthesia. All patients were routinely given antibiotics to reduce the chances of graft infection and to obtain uniform groups.

Subcutaneous infiltration of the study medications was done immediately after harvesting the graft to avoid edema or hematoma to the graft itself. Injection was through vertical lines 2 cm apart by 25 G×90 mm K-3 lancet.

Outcomes

The primary outcome was Donor-site pain measured hourly during the first postoperative 12 hours through use of a numeric rating scale (NRS). The patients were asked to mark their donor-site pain on a scale graded from 0 to 10, where 0 indicated no pain and 10 was maximum pain.

The secondary outcome was the cumulative consumption of morphine or morphine equivalents during the first postoperative 12 h, and time from end of surgery until first breakthrough pain.

End of surgery was defined as time point 0. Morphine was administered using intravenous patient-controlled analgesia (PCA), 0.05 mg/kg demand dose and 10-min lockout interval. Time to first breakthrough pain was defined as the time from end of surgery to the first PCA dose.

Patients were instructed to use PCA when numeric rating scale (NRS) pain score exceeds 3. Fentanyl was administered as a 0.8 µg/kg demand dose and 5-min lockout interval, if morphine was not tolerated. The nurses were instructed to administer intravenous fentanyl if the patients had not sufficient pain control from the PCA. Additional opioid consumption was documented in the patient's medical record. Intravenous fentanyl given was converted to intravenous morphine equivalents for the calculation of 12-h opioid consumption. Fentanyl/morphine equivalent ratio is 100 mcg: 10 mg.

Data capture

Data were collected by the anesthesia doctors and nurses, who were all blinded to allocated study group.

Statistical analysis

Data analysis was performed using SPSS Package (IBM Corp. 2012. Version 21.0. NY, USA). Normally distributed numerical values were compared using the independent Student's *t* test "presented as mean ± SD," data that do not follow normal distribution were analyzed using Mann-Whitney test "presented as median (IQR)." Fisher exact test or the χ^2 test was used for analysis of categorical variables.

Results

All 95 patients finished this study. All the subcutaneous infiltrations were successful with a satisfactory level of anesthesia and all of the data were analyzed (Fig. 1).

Demographic data (Table 1)

The mean age of the study population was comparable for both groups. The primary characteristics of both groups (age, sex, ASA status, and BMI), were comparable, with no significant differences observed.

Regarding numerical rating scale for pain sensation, data analysis revealed statistically significant differences ($P < 0.05$) across the first 7 h postoperatively, with LB group subjects experiencing greater pain than LB + D group. There were some outliers in both groups that were represented with either an asterisk (*) for LB group, or a dot (●) for LB + D group. Starting from the 8th hour postoperatively onwards to the 12th hour, NRS values were comparable for both groups (Fig. 2).

Numerical rating scale

Similarly, total dose of morphine (including morphine equivalent doses) in milligrams was significantly higher in LB group than LB + D group, as well as the time from end of surgery to occurrence of first breakthrough pain was considerably sooner in LB group than LB + D group.

No significant differences were noticed as regards duration of surgery between both groups (Table 2).

Discussion

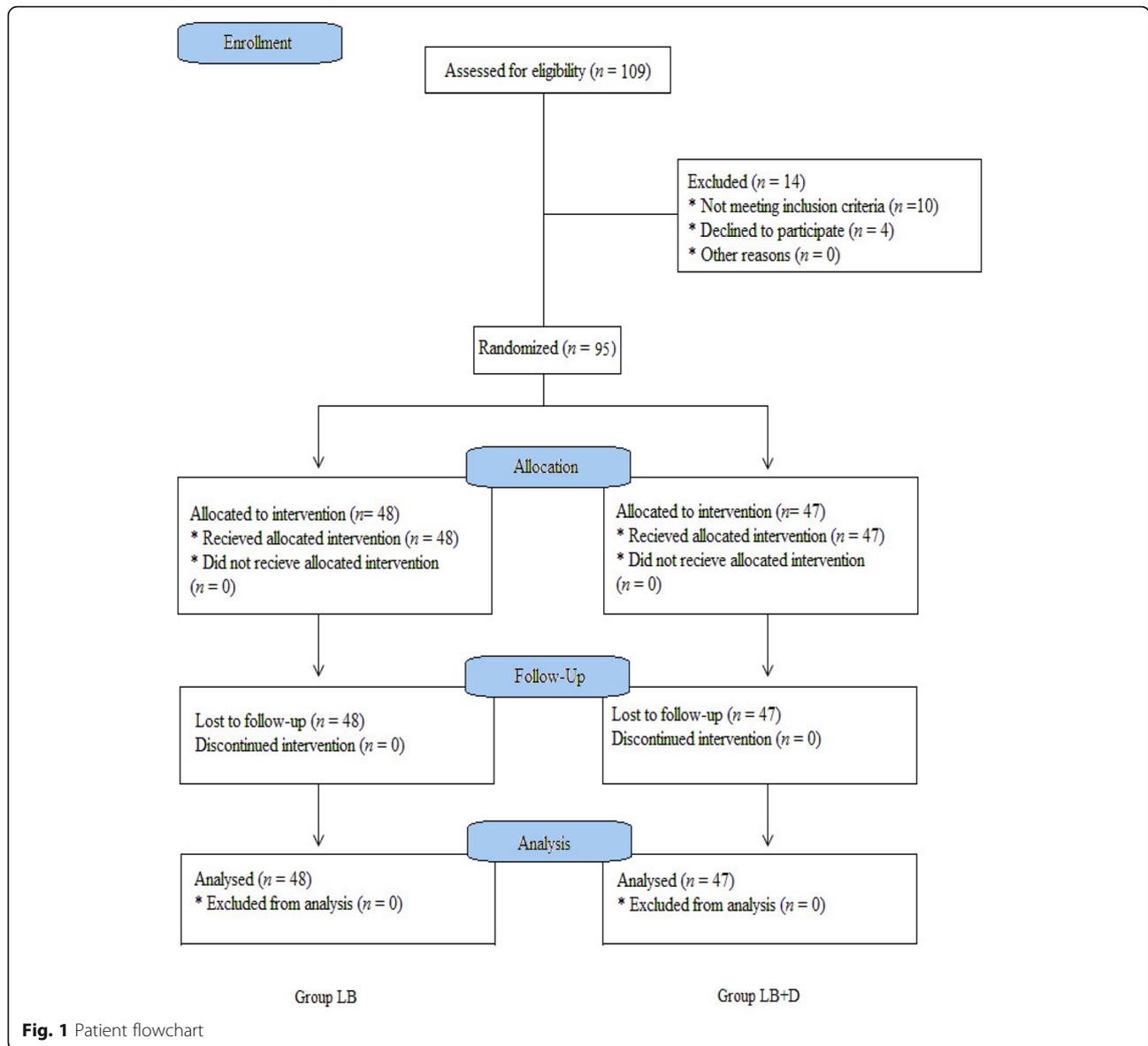
This study demonstrated that subcutaneous infiltration of skin graft donor sites with bupivacaine-dexamethasone mixture was superior to bupivacaine alone as regards numerical rate of pain sensation, time to first breakthrough pain postoperatively, and total dose of morphine consumption.

Of all the adverse effects in the healthcare environment, pain is singled out to be the most serious, necessitating prompt intervention. It has serious sequelae such as impaired body function, systemic pain related morbidities, increased length of hospital stay leading to greater risk of nosocomial infections that, if not properly managed, will evolve to chronic pain (Rawal 2008).

The conventional approach of managing postoperative pain was the widespread use of non-steroidal anti-inflammatory agents and/or opioids, which had their own risks including gastrointestinal bleeding, vomiting, sedation, and respiratory depression (Maund et al. 2011).

Wound infiltration is increasingly being used in the intra- and postoperative setting where local anesthetics are used alone or in conjunction with other additives. The rising interest in these techniques can be attributed to simplicity, reduction in opioid and NSAID requirement, and better safety profile.

The mechanisms by which local anesthetic wound infiltration act include decreased nociceptive pain afferents of the wound surface and suppression of local inflammatory response. The latter leads to pain and hyperalgesia (Hahnenkamp et al. 2002).



Blome-Eberwein et al. compared epinephrine/saline/lidocaine + ropivacaine mixture versus saline-only injection. They randomly assigned their patients into two groups: one group received the former modified tumescent solution, the other warm saline injected subcutaneously before

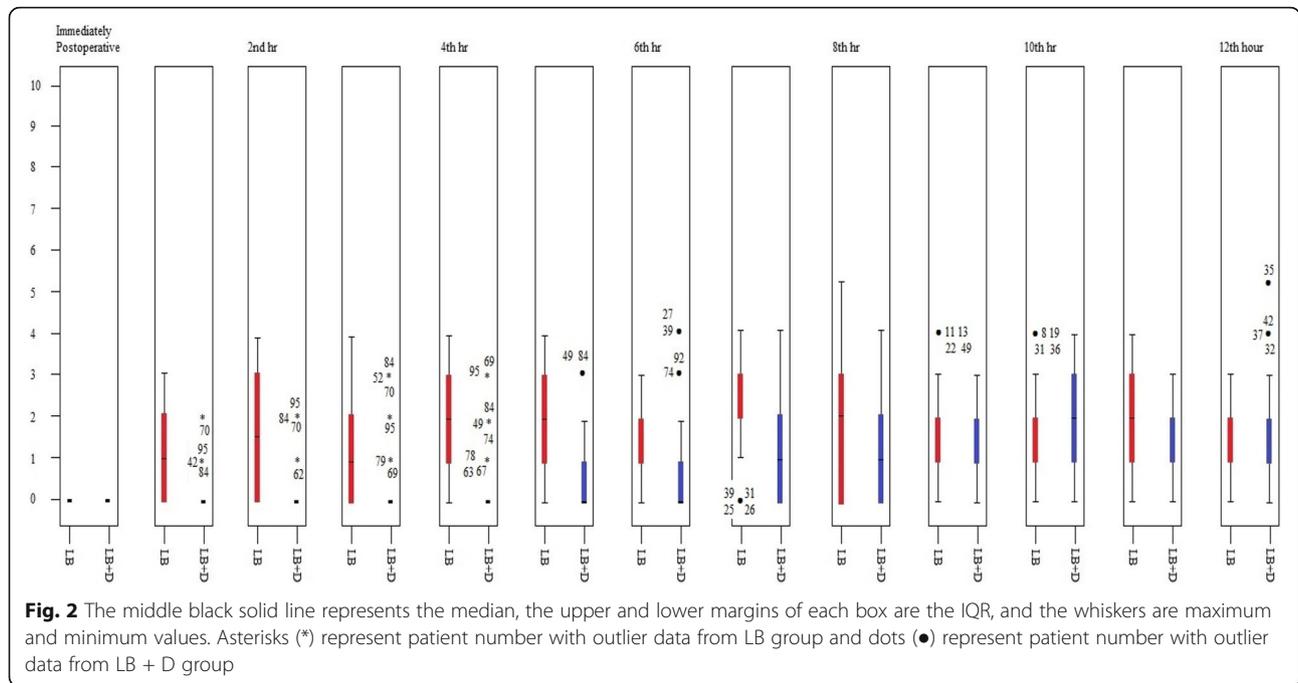
harvesting donor skin with a dermatome. They measured pain, pruritus and skin perfusion postoperatively. They did not find any significant differences between either groups with respect to postoperative pain relief and thus did not recommend their techniques to be universally adopted (Blome-Eberwein et al. 2013).

Table 1 Demographic data

	Group LB (n = 48)	Group LB+D (n = 47)	p value
Age(in years)	44.43 ± 15.4	45.5 ± 13	0.715
ASA(I/II)	24/24	24/23	0.490
Sex(M/F)	23/25	23/24	0.486
BMI(kg/m2)	27.5 ± 3.74	26.6 ± 3.8	0.247

Data are presented as mean ± SD or ratio p > 0.05 is considered statistically non-significant

Goodacre et al. compared the analgesic efficacy of topically applied EMLA cream versus subcutaneous infiltration of lidocaine 0.5% plus adrenaline 1:200,000. They used the visual analogue score VAS and the verbal ratings score, both failed to show statistically significant differences for postoperative pain. They attributed this to lack of matching in mean area of graft harvested, in the EMLA group the area was 122.4 cm², while in the infiltration group it was 69 cm². Thus, leading to discrepancy in pain



assessment due to unmatched harvested area (Goodacre et al. 1988).

The results of this study demonstrated that the addition of dexamethasone to bupivacaine decreased postoperative pain leading to significant reduction in the amount of opioids consumed.

The mechanisms underlying the analgesic effects of corticosteroids are not clear yet. Their effect is presumed to be mediated by anti-inflammatory effects and local immunosuppressive action. Topical steroids have vaso-pressor effect which is mediated by classical glucocorticoid receptors. Steroids act by binding to intracellular glucocorticoid receptors thereby regulating nuclear transcription. Furthermore steroids may have direct effect on nerve endings which may explain dexamethasone analgesic action (Jabalamel et al. 2015).

In our study, regarding numerical rating scale for pain, group (LB + D) showed significantly pain relief across all time intervals compared to group (LB). The total dose of morphine was also significantly less in group (LB + D)

than group (LB). As well as the time to first breakthrough pain.

Literature regarding addition of steroids to subcutaneous infiltration in donor site of graft surgery is lacking, but it is reported to be successful in local infiltration for other surgical sites.

JU and colleagues compared a mixture of ropivacaine-dexamethasone and ropivacaine only for postoperative infiltration in tonsillectomy and adenoidectomy. They recorded pain scores at different intervals from 4 to 24 h postoperatively, and found significantly better results for dexamethasone addition in terms of pain assessment scores, total analgesic intake, nausea and vomiting, and discharge from hospital (Ju et al. 2013).

Similarly, Ikeuchi et al. compared ropivacaine-dexamethasone to ropivacaine alone in total knee arthroplasty operation and found a significant decrease in postoperative pain severity in the steroid group than local anesthesia only group. Moreover, they investigated the level of inflammatory markers C-reactive protein and

Table 2 Total dose of Morphine Consumption, time from end of surgery to 1st breakthrough pain and duration of Surger

	Group LB (n = 48)	Group LB+D (n = 47)	p value
Total dose Of morphine consumption(including morphine equivalent doses) (mg)	9.55 ± 4.47	1.92 ± 2.85	* < 0.001
Time from end of surgery to 1st breakthrough pain (h)	2.66 ± 0.91	8.34 ± 1.57	* < 0.001
Duration of surgery (min)	51.49 ± 8.44	52.3 ± 8.07	0.914

Data are presented as mean ± SD, *p < 0.001 is considered statistically significant

interleukin 6 in the drainage fluid which they reported were less in steroid group (Ikeuchi et al. 2014).

Results from above studies cannot be readily extrapolated to skin donor site in graft surgeries, but at least show the potential benefit of steroids addition to local anesthetic infiltration protocols, and highlight the importance of conducting further quality trials.

Limitations to this study include short study period of 12 h postoperatively, the subjective nature of pain assessment in the recruited individuals, and the lack of continuous replenishment of local anesthetic infiltration, which resorts patient caregivers resort to use of oral pain relief medication once the effect of local analgesia wanes, the latter have their own well-documented risks.

Several improvements to the study can be proposed, such as extending the study observation period to 48–72 h, use of elastomeric pumps to deliver a constant rate of local anesthesia flow; these devices need subcutaneous catheters which can be placed intraoperatively, and lastly the inclusion of objective ways of pain assessment such as biological markers which include serum cortisol, free fatty acid, and plasma adrenaline among others is suggested to improve the quality of future study designs.

Conclusion

In brief, the use of dexamethasone as adjuvant to bupivacaine in local anesthetic infiltration regimens for partial thickness skin donor graft sites was superior in terms of better pain relief and less need of rescue analgesia in the early postoperative period, to bupivacaine alone.

Acknowledgements

Not applicable.

Authors' contributions

RM provided the acquisition of data, did the analysis and interpretation of the data, and drafted the manuscript. AM contributed to the data interpretation, and drafted and revised the manuscript. AA contributed to the study conception and design and in the acquisition of data. RM drafted and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All datasets used and/or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This randomized controlled study was approved by Ain Shams University Research Ethics Committee (REC) (FMASU R75/2018) and written informed consent was obtained from all the patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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