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ORIGINAL INVESTIGATION

Perineural low dexamethasone dose as adjuvant in supraclavicular brachial plexus block for arteriovenous fistula creation in end stage renal disease: a randomized controlled trial

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Abstract

Background and aims: Dexamethasone as adjunct to local anesthetic solution improves the quality of brachial plexus block (BPB). However, evidence for its efficacy at low doses (< 4 mg) is lacking. This study was designed to evaluate the duration of analgesia attained with low dose dexamethasone as adjuvant to local anesthetic for creation of arteriovenous fistula (AVF) under BPB.

Methods: Sixty-six patients scheduled for AVF creation were randomly allocated to receive either saline (control) or 2 mg dexamethasone, together with 0.5% ropivacaine and 0.2% lignocaine. The primary outcome was duration of analgesia, defined as time from performing the block to the first analgesic request. The secondary outcomes were time from injection to complete sensory block, time from injection to complete motor block, duration of motor block, postoperative analgesic consumption, and fistula patency at three months.

Results: All the blocks were effective. In the group that received dexamethasone, the time to first analgesic request was significantly delayed (432 ± 43.8 minutes vs. 386.4 ± 40.2 minutes; $p < 0.01$). The onset of sensory and motor blockade occurred faster in dexamethasone group and overall analgesic consumption was also reduced. However, dexamethasone addition did not prolong the duration of motor block. There was no statistically significant difference in the patency of fistulas between the two groups at three months. ($p = 0.34$).

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Conclusion: Addition of low-dose perineural dexamethasone to local anesthetic solution significantly prolonged the duration of analgesia. Further trials are warranted to compare the adverse effects between dexamethasone doses of 4 mg and lower.

Introduction

There has been a considerable evolution in the practice of regional anesthesia over the past few decades. Regional anesthesia improves the quality of perioperative pain management. Although the single-injection regional anesthesia technique is easy to perform and requires fewer resources and manpower during postoperative management, its benefits may be offset by its limited duration of analgesia. This limitation of the single-injection technique can be overcome by the use of adjuvants along with local anesthetics, which may serve the purpose of prolonging the postoperative analgesia. Furthermore, a good quality postoperative analgesia ensures patient satisfaction, decreases duration of hospital stay, and decreases the occurrence of chronic pain and its related complications.

The efficacy of dexamethasone as a perineural adjunct to local anesthetics in prolonging the duration of analgesia has been validated by several prior systematic reviews and meta-analyses.[1-5] Various doses of dexamethasone have been used in studies ranging from 4 mg to 10 mg, without a clear rationale for using a particular dose. The use of dexamethasone may also result in complications like hyperglycemia, immunosuppression, infection, suppression of hypothalamic-pituitary axis, impaired wound regeneration, neurotoxicity, amongst others — which may be dose-dependent in nature.[6] Furthermore, there is lack of evidence to suggest that higher perineural doses of dexamethasone are more efficacious compared to lower doses.[7]

In contrast to this, a recent meta-analysis by Kirkham et al.[5] showed a ceiling dose of 4 mg for perineural administration. Few authors have studied perineural dexamethasone administration at doses lower than 4 mg, and therefore robust evidence for doses less than 4 mg is lacking.

The objective of this randomized controlled trial was to evaluate the duration of analgesia attained with 2 mg dexamethasone as an adjuvant to local anesthetic solution in ultrasound guided brachial plexus block (BPB) in patients with chronic kidney disease (CKD) undergoing arteriovenous fistula (AVF) creation. We hypothesized that a lower perineural dose of dexamethasone also significantly prolongs the duration of analgesia of supraclavicular BPB.

Methods

This prospective, double-blind, randomized study was conducted after obtaining approval by the Institutional Ethics Committee (IEC 9606/PG 2Trg/2013/14301). Written informed consent was obtained from the patients enrolled in the study. Sixty-six patients of either gender, aged 18—60 years, belonging to American Society of Anesthesiologists (ASA) physical status II and III, and scheduled for arteriovenous fistula (AVF) creation were studied from June 2014 to November 2016. Non-inclusion criteria were: uncooperative patients or patient refusal, clinically significant coagulopathy, presence of upper extremity peripheral neuropathy/neurological disorder, presence of local site infection, history of known allergy to local anesthetics, body mass index less than 18 or more than 25, revision of previously blocked AVF, contraindication for brachial block like anatomical deformities, history of cephalic vein or central vein occlusion, and brachial or radial artery stenosis.

The enrolled patients were randomly allocated by a computer- generated sequence into two groups — group RL and group RLD. Sealed opaque envelopes with the group allocation were opened by an anesthesiologist not involved in the study, who prepared the drug solutions for the block. Patients allocated to group RL (n = 33) received BPB using 0.5% ropivacaine (Ropin, Neon Laboratories Ltd., Mumbai, India) 1 $mg.kg^{-1}$, 2% lignocaine (Lox, Neon Laboratories Ltd, Mumbai, India) 2 $mg.kg^{-1}$, and 2 mL normal saline. Patients in group RLD (n = 33) received BPB using 0.5% ropivacaine (1 $mg.kg^{-1}$), 2% lignocaine (2 $mg.kg^{-1}$) and 2 mg preservative-free dexamethasone diluted in 2 mL normal saline.

The patients were evaluated prior to surgery and were explained about the anesthetic procedure. Monitoring consisted of standard ASA monitors — electrocardiography, non-invasive blood pressure, pulse oximetry, and temperature. Pre-procedural vitals were recorded. Using strict aseptic precautions, a sterile 6—13 MHz linear US (ultrasound) transducer (SonoSite; M-Turbo; SonoSite; Bothell, Washington, USA) was used to visualize the brachial plexus in supraclavicular region. Brachial plexus was recognized by its characteristic "honeycomb appearance" in the region lateral to the subclavian artery. After infiltrating the skin with local anesthetic, a 22G, 50-mm, insulated needle (Stimuplex A; B Braun, Melsungen, Germany) was inserted in an "in plane technique" to reach the lateral corner of the subclavian artery and above the first rib. A small volume of local anesthetic solution (0.5—1 mL) was injected initially to hydrodissect the fascial sheath and perineural structures. With the needle tip near the brachial plexus, drug solution was injected in aliquots with intermittent aspiration until the entire plexus was encircled by the solution. Sensory block was evaluated by a blunt-tipped needle every five minutes at 5, 10, 15, and 20 minutes after injection in the region of distribution of the following nerves as: median (palmar aspect of the second finger), ulnar (fifth finger), radial (dorsum of the hand between the thumb and second finger), musculocutaneous (lateral forearm), and medial cutaneous nerve of the forearm (medial forearm). A validated 3-point scale was used: 0 = no block (patient has normal sensation); 1 = patient can feel pin prick, but the sensation is reduced compared with the unblocked side; and 2 = complete anesthesia. The combined score of sensory blockade of the 5

nerves was calculated. The patient was considered to have a satisfactory sensory block when a minimal score of 9/10 was achieved. Motor blockade was evaluated by the modified Bromage score[8] for upper limb: 0 = normal motor function with full extension and flexion of elbow, wrist, and fingers; 1 = decreased motor strength, with ability to move only fingers; 2 = complete motor block with inability to move elbow, wrist, and fingers. A successful block was one with adequate sensory blockade and the patient being able to tolerate a simulated surgical stimulus. The need to give additional local anesthetic infiltration or general anesthesia constituted a failed block. Intraoperative hemodynamics were recorded every five minutes.

Visual Analog Scale (VAS) was used by a blinded investigator to assess postoperative pain at 1, 2, 4, 6, 8, 12, and 24 hours after surgery. Oral paracetamol 500 mg was administered when VAS score exceeded 4. If the pain was not relieved with a repeat dose of paracetamol, then patients were administered tablet tramadol 100 mg per oral. The analgesic doses given were recorded. Time to return of motor power was assessed by the patient's ability to abduct the shoulder. Any adverse events like hypotension (a 20% decrease in relation to the baseline value), bradycardia (HR $<$ 50 beats per min), hypoxemia ($SpO_2 < 90\%$), nausea and vomiting, vascular puncture, inadvertent IV (intravenous) injection, significant eye drooping (Horner syndrome), hematoma formation, local anesthetic toxicity, pneumothorax, and dyspnea were recorded. The patients were discharged home after 24 hours and interviewed by telephone after 48 hours for the presence of any complications.

During a follow-up visit after three months, the patency of AV fistula was assessed by placing a Doppler probe over the target vessels and observing for blood flow. The measurements of blood flow through the vessels were recorded only after stabilization of signal for at least 30 seconds. Minimum of two readings were obtained.

The primary outcome was the duration of analgesia, defined as the time from performing the block to the first analgesic request. The secondary outcomes were time of onset of sensory block (defined as the time from injection to complete sensory block); time of onset of motor block (defined as the time from injection to complete motor block); duration of motor block (injection to full ability to abduct the shoulder); overall postoperative analgesic consumption; and AVF patency at three months as assessed by Doppler ultrasound.

All observations were recorded in a standardized data collection sheet and analyzed statistically using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 17.0 for Windows). Qualitative or categorical variables were described as frequencies, percentages and proportions. The association of categorical data with the two groups was analysed using Chi-square test or Fisher's exact test, whichever applicable. The normality of quantitative data was assessed using Kolmogorov-Smirnov test of normality. Quantitative variables were described in terms of mean and standard deviation when normally distributed and median and quartiles if non-normally distributed. For normally distributed quantitative data, Student's *t*-test (unpaired) was applied to compare two group means. For skewed data, Mann-Whitney U Test was applied to compare the distributions of two groups. For time related comparisons within groups, repeated measure ANOVA test was used, followed by post hoc multiple comparisons test (Bonferroni correction). The duration of analgesia was analysed by the Kaplan-Meier survival analysis. A p-value < 0.05 was considered as significant.

The calculated sample size was 23 patients per group based on expected improvement of analgesia duration by 30% at $p < 0.05$ and power goal of 90%. With a dropout rate of 40%, the minimum number of patients to be studied came out to be 33 patients in each group.

Results

Sixty-six patients were enrolled and randomized out of 70 patients who were assessed for the study (Fig. 1). All the patients completed the study. The data was analyzed and

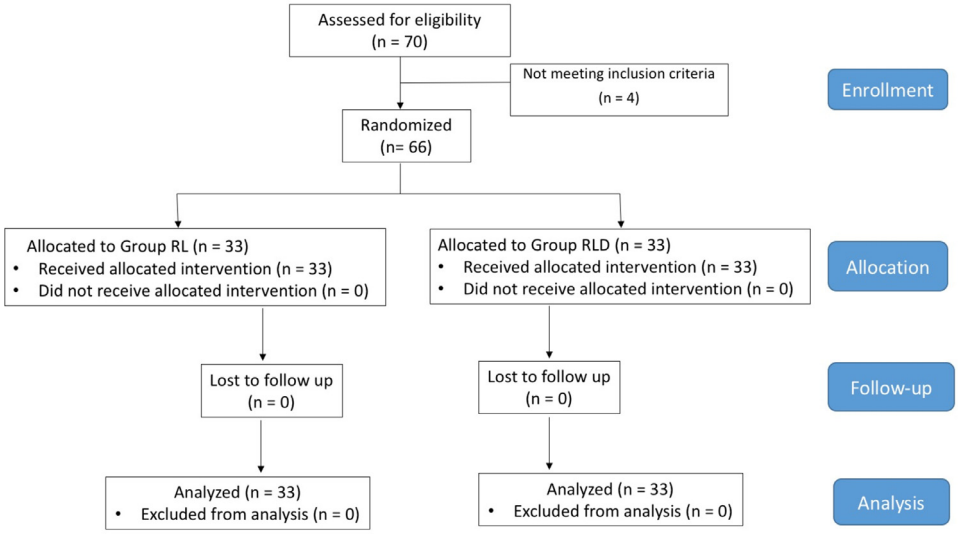


Figure 1 CONSORT flow diagram of participants enrolled in the study.

Table 1 Patient characteristics.

	Group RL n = 33	Group RLD n = 33
Age (years)	46.1 ± 15.7	46.2 ± 12.2
Gender (male/female)	18/15	21/12
Height (cm)	161.5 ± 5.1	162.1 ± 4.9
Weight (kg)	63.6 ± 6.4	64.3 ± 4.7
Duration of surgery (min)	90.8 ± 19.4	99.1 ± 17.1
Duration of anesthesia (min)	258.5 ± 76.4	263.6 ± 74.6

All results are expressed as mean ± SD.

Table 2 Blockade characteristics.

	Group RL	Group RLD	*p*-value
Time to onset of sensory block	6.2 ± 1.1 min	5.3 ± 1.0 min	< 0.01[a]
Time to onset of motor block	6.7 ± 1.4 min	3.2 ± 0.9 min	< 0.01[a]
Duration of sensory block	386.4 ± 40.2 min	432 ± 43.8 min	< 0.01[a]
Duration of motor block	236.5 ± 32.4 min	250.0 ± 37.8 min	0.07

All the values are expressed as mean ± SD.
[a] $p < 0.05$.

the baseline characteristics were found to be comparable between the two groups (Table 1).

The addition of low dose dexamethasone to a combination of ropivacaine and lignocaine resulted in a faster onset of sensory blockade (5.3 ± 1.0 min vs. 6.2 ± 1.1 min; $p < 0.01$). Dexamethasone also hastened the onset of motor blockade (3.2 ± 0.9 min vs. 6.7 ± 1.4 min; $p < 0.01$). (Table 2)

The duration of analgesia was also prolonged with the addition of dexamethasone (432 ± 43.8 min vs. 386.4 ± 40.2 min) which was statistically significant ($p < 0.01$). The pain-free probability with time after performing the block was significantly higher in the dexamethasone group (log rank test, $p < 0.001$) (Fig. 2). However, dexamethasone did not prolong the duration of motor blockade significantly (250.0 ± 37.8 min vs. 236.5 ± 32.4 min; $p = 0.07$). (Table 2)

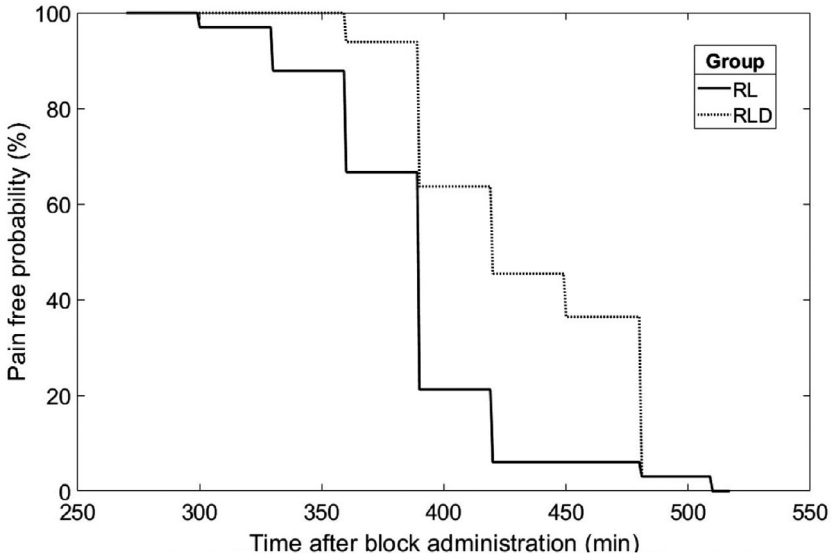
The pain (VAS) scores of the two groups were comparable up to four hours postoperatively after which lower VAS scores were observed in the RLD group compared to RL group (Table 3). The VAS score was significantly less in RLD group compared to RL group at 6 hours ($p < 0.01$) and 8 hours ($p = 0.02$) postoperatively.

In the RLD group, 7 patients did not request for any postoperative rescue analgesic, 26 patients requested for rescue analgesic once, and no patient required a second dose of rescue analgesic. In the RL group, all patients requested for postoperative rescue analgesia out of which 28 patients

Table 3 Postoperative pain scores (VAS) at different time points.

Time	Group RL	Group RLD	*p*-value
VAS 1 h	0 (0,0)	0 (0,0)	1.00
VAS 2 h	0 (0,0)	0 (0,0)	0.32
VAS 4 h	1.06 (1,0)	0.82 (1,1)	0.18
VAS 6 h	2.88 (3,2)	2.12 (2,2)	0.002[a]
VAS 8 h	3.27 (3,1)	2.76 (3,1)	0.016[a]
VAS 12 h	1.58 (2,1)	1.42 (1,1)	0.19
VAS 24 h	1.06 (1,0)	1.0 (1,0)	0.71

All the values are expressed as median (IQR).
[a] $p < 0.05$.



Group RL- Ropivacaine, lignocaine and normal saline
Group RLD- Ropivaciane, lignocaine and dexamethasone

Figure 2 Duration of analgesia: Kaplan-Meier survival curve depicting the cumulative pain-free probability as a percentage in both groups after performing the block.

requested only once while 5 patients requested second dose of rescue analgesia. No patient in either of the groups requested for a second rescue analgesic. There was statistically significant difference regarding overall analgesic consumption between the two groups (p = 0.01). However, addition of dexamethasone had no impact on the outcome of the fistula and the difference in the flow in the fistula between the two groups was not statistically significant (p = 0.34).

Discussion

The results of this prospective, randomized study concluded that the addition of low dose dexamethasone to a combination of ropivacaine and lignocaine hastened the onset of sensory and motor blockade while simultaneously prolonging the duration of analgesia in AVF construction surgery. This study also demonstrated better postoperative pain relief and lesser postoperative rescue analgesic consumption in the group which received dexamethasone.

Supraclavicular brachial plexus block provides rapid, dense, and predictable anesthesia of the entire upper extremity in a very consistent manner. Ultrasound guidance for supraclavicular block reliably reduces the procedure time and improves the safety profile of the technique.[7] Occasionally, a single-shot technique for peripheral nerve block may prove inadequate to provide pain relief in postoperative period. Perineural catheters have been used to extend the duration of analgesia, but these may be associated with problems like difficulty in catheter placement, catheter migration, infection, anesthetic drug leakage, or pump malfunction requiring complex logistic organization, especially following ambulatory surgery.[9] This led to the use of various adjuvants to prolong the duration of analgesia administered by a single-shot technique thereby avoiding the use of continuous perineural infusions.[10-12]

Corticosteroids like dexamethasone have been used routinely for chronic pain management by administration into the epidural space for treating radicular pain with a reliably acceptable side effect profile.[13] There are various theories regarding the mechanism of action of dexamethasone as an adjuvant to local anesthetics in regional anesthesia. Steroids induce a degree of vasoconstriction, so one theory is that the drug acts by reducing local anesthetic absorption.[14] A more attractive theory holds that dexamethasone increases the activity of inhibitory potassium channels on nociceptive C-fibers (via glucocorticoid receptors), thus decreasing their activity.[15] Due to concern of adverse physiochemical effects from perineural dexamethasone, certain authors have recommended against its use as an adjuvant to LA or have suggested that alternative routes of administration (IV) are preferable.[16] Several studies have used varying doses of dexamethasone ranging from 4 mg to 10 mg, hence an optimum dosing regimen remains undefined. Despite the concern surrounding the "off-label" use of perineural adjuvants, the safety profile of dexamethasone is promising.

The current study demonstrated prolongation of duration of analgesia in patients receiving 2 mg perineural dexamethasone as adjunct to local anesthetic. Previous studies have also successfully demonstrated that lower doses of dexamethasone ranging from 1—4 mg are equally effective as analgesics in the perioperative period.[17-20] We found a similar duration of motor blockade in dexamethasone and control groups, in contrast to the findings of Liu[17] and Albrecht et al.[19] They may have observed a different duration of motor blockade possibly due to various reasons. Firstly, the patients studied by Liu and Albrecht et al. underwent shoulder arthroscopy and required shoulder immobilization in the postoperative period, which may probably compromise the motor function recovery evaluation. Secondly, the motor function was evaluated by a telephonic call to the patient at home in the above-mentioned studies. This subjective assessment of motor function recovery may be inaccurate due to recall bias. The prolonged analgesia without prolongation of motor blockade is desirable in our patient population since AVF construction is performed as an ambulatory surgery in our center. It is beneficial for the patient, surgeon, as well as the anesthesiologist since it allows early discharge and reduces hospital costs and wastage of manpower. Our study also revealed better pain-related outcomes in patients receiving dexamethasone in the form of lower postoperative pain scores and lesser requirement of rescue analgesia. Our study demonstrated longer time to first analgesic request in dexamethasone group, which was similar to the findings of Woo et al.[18] However, a few other studies were unable to detect any clinically significant difference in postoperative pain scores and analgesic requirement in patients receiving dexamethasone.[17,19,20] This may be attributed to the heterogeneity in type, volume, and dose of local anesthetic drugs as well as the level of blocks administered in the studies.

Although the difference in duration of analgesia between the two groups in our study was statistically significant, the actual difference in duration was less than 1 hour. The percentage difference was 15%, which was much less than the expected difference of 30% used in our sample size calculation. In their systematic review and meta-analysis of nine randomized trials, Choi et al.[1] found that higher doses of perineural dexamethasone in the range of 4—10 mg when mixed to the long-acting local anesthetics could prolong the duration of analgesia by almost 9 to 10 hours. The use of lower doses like 1—3 mg has shown varying results by prolonging the analgesia duration by a wide range of 2.5—11 hours.[17-19] The use of lower doses may not always provide a clinically significant effect, sometimes it may only provide a subtle and marginal benefit, similar to what was observed in our study. The prolongation of analgesia provided by perineural dexamethasone seems to be dose dependent. Since Kirkham et al.[5] found that perineural dexamethasone reaches a ceiling effect after a 4-mg dose, it may be preferable to use 4-mg dose as deemed effective in their metanalysis. The systemic adverse effects of dexamethasone, like hyperglycemia, immunosuppression, and neurotoxicity, were not assessed in our study. If the use of doses < 4 mg has similar incidence of adverse effects, it would be better to use a standard dose of 4 mg as it guarantees a longer analgesic duration. On the contrary, if lower doses produce fewer adverse effects, the anesthesiologist may weigh the risk-benefit ratio of administering lower dexamethasone doses in this susceptible patient population.

We found that both groups had similar low VAS scores throughout the 24 hours of assessment. Although we found a statistically significant difference in VAS scores at 6- and 8-

hour intervals, this may or may not be clinically relevant since the absolute difference in VAS pain scores was less than 1 point between the groups. The absolute value of the minimal clinically important difference in pain severity continues to be debatable, but values varying between 0.9 and 1.1 on VAS scale have been reported to be clinically significant.[21,22] We chose to use the VAS scale as it is practical, reproducible, and sensitive to treatment effects. Even though small differences in scores may reach statistical significance during analysis, statistical significance cannot be equated with clinical significance. For the clinicians, it is the actual clinical impact on patients' pain that is more important.

Predicting the factors that contribute to maturation of AVF remains challenging. This is due to the heterogeneity of ESRD patients studied, and also due to the varied etiologies of ESRD. AVF maturation may also be influenced by several other factors, like patient's comorbid illnesses including — but not limited to — peripheral vascular disease and diabetes mellitus, which occur concurrently in patients with chronic kidney disease.[23] As concluded by Reynaud et al. in their study, BPB leads to significant intraoperative forearm vasodilation, but does not result in improved distal AVF prevalence or outcomes when compared to the conventional techniques.[24] In our study, there was no statistically significant difference on adding dexamethasone to the flow characteristics of the fistulae. Also, of all the 66 patients recruited in the study, all the fistulas except one were patent at the three months follow up. The good outcome may be attributed to the meticulous preoperative site selection using ultrasound, which was done for all the patients enrolled in the study. It may also be attributed to the administration of BPB, which has shown to improve AVF outcomes.[25,26] A larger sample size is, however, warranted to evaluate the long-term clinical benefits of addition of dexamethasone. It may also be advisable to follow these patients for a longer time to accurately assess the patency of fistula before drawing conclusions about the long-term patency.

There were some limitations in the study. Firstly, the sample size may be inadequate to decide if the perineural dexamethasone as an adjuvant in brachial plexus block can actually affect the fistula outcome. Secondly, the three months follow-up period may be insufficient to conclude whether the intervention actually resulted in a meaningful outcome. Longer follow-up periods are desired to achieve more definitive results. Thirdly, although the fistulas were created by surgeons with at least five years of surgical experience, surgeries performed by different surgeons or by different operative technique may have an impact on the outcome of the fistula. Fourthly, the maturation of the fistulas is also affected by patient-related factors like underlying comorbidities which were not assessed.[27,28] Another possible limitation of this study is that it is possible for the patients to have late-onset neuropathy with the use of perineural dexamethasone, which was not assessed as the patients were not followed beyond three months postoperatively. For future investigations, it is suggested to follow up these patients for longer durations using survey questionnaires or telephonic interviews to detect such complications.

To conclude, there is no randomized controlled trial conducted to assess the efficacy of low-dose dexamethasone as an adjuvant to local anesthetic agent for creation of an arteriovenous fistula to the best of our knowledge. The lower dose of dexamethasone seems to provide a subtle and marginal prolongation of duration of analgesia and may improve patient comfort and satisfaction in the postoperative period. However, it may be prudent to use dexamethasone doses < 4 mg only if it has lower incidence of adverse effects compared to doses of 4 mg and higher, as lower doses may be accompanied by the disadvantage of clinically insignificant pain relief in the postoperative period. Hence, future studies aimed at comparing the incidence of adverse events between perineural dexamethasone doses of 4 mg and 2 mg may resolve this existing conundrum for the anesthesiologist.

Conflicts of interest

The authors declare no conflicts of interest.

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