Randomized Trial

Analgesic Effect of Nalbuphine When Added to Intravenous Regional Anesthesia: A Randomized Control Trial

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Background: Different adjuvant drugs are currently added to lidocaine for intravenous regional anesthesia (IVRA) to decrease tourniquet and postoperative pain.

Objective: The aim of the study was to examine the effect of nalbuphine when added to IVRA.

Study Design: Prospective, randomized, double-blind, controlled clinical trial.

Setting: Assiut University Hospitals.

Methods: One hundred-six adult patients scheduled for unilateral hand surgery under IVRA were randomized into 2 equal groups. The lidocaine-nalbuphine (LN) group received nalbuphine plus lidocaine and the lidocaine (L) group received lidocaine. A tourniquet and postoperative pain were assessed using a visual analogue scale (VAS). The following parameters were measured: onset and recovery time for both sensory and motor blocks, intra- and postoperative analgesic consumption, time to first analgesic request, postoperative nausea and/or vomiting (PONV), hemodynamics, and cortisol levels.

Results: Early tourniquet and postoperative pain were significantly lower in the LN group. The onset time for both sensory and motor blocks was significantly shorter in the LN group. In addition, the recovery time for both sensory and motor blocks was longer in the LN group. Intra- and postoperative fentanyl consumption was significantly lower in the LN group with no significance in postoperative diclofenac consumption. The patient first analgesic request was significantly delayed in the LN group ($P < 0.0001$). There were no significant differences between the 2 groups in PONV, hemodynamic parameters abnormalities, medications adverse events or cortisol levels.

Limitations: The inclusion of a study group in which the nalbuphine administered systemically could determine whether its beneficial effects were due to its local or systemic action.

Conclusions: Nalbuphine decreases early tourniquet and postoperative pain after IVRA and delays the need for analgesic rescue. In addition, nalbuphine accelerates the onset and prolongs the recovery time for both sensory and motor blocks with no significant adverse events. However, it has no effect on postoperative cortisol levels.

Key words: Intravenous, regional anesthesia, lidocaine, nalbuphine, pain, postoperative

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Intravenous regional anesthesia (IVRA) with lidocaine has been used for decades to facilitate surgery on the hand and forearm. It has the advantages of high accuracy and success rate, rapid onset of action, as well as providing a bloodless surgical field. Tourniquet pain during surgery, short duration of postoperative analgesia, and local anesthetic toxicity limit its use. Different adjuvant drugs were added to prolong

postoperative analgesia such as tramadol (1), ketorolac (2), dexmedetomidine (3), ketamine (4), and nalbuphine (5). Nalbuphine is a semi-synthetic opioid analgesic, primarily a kappa agonist and partial mu antagonist. Because nalbuphine holds both agonist and antagonist activities, it has a better safety profile with fewer side effects, such as pruritus and respiratory depression, compared to other opioids (6,7). We hypothesized that the addition of nalbuphine to lidocaine in IVRA would minimize tourniquet pain and prolong postoperative analgesia. This study was planned to compare the effect of the addition of nalbuphine to lidocaine on the tourniquet and postoperative pain. Secondary outcome measures included onset and recovery time of sensory and motor blocks, the time to first analgesic request, postoperative nausea and/or vomiting (PONV), hemodynamic changes, and the effect of nalbuphine on cortisol level.

Methods

This randomized, controlled, double-blind study was carried out after the approval from the research ethics boards of Assiut University hospitals and receiving written informed consent from each participant. The trial was registered in ClinicalTrial.gov (ClinicalTrials.gov ID: NCT02678585). One hundred-six adult patients with American Society of Anesthesiologists (ASA) physical status I – II, age between 20 and 50 years old, scheduled for elective unilateral hand surgery were included in this study. Exclusion criteria included allergy to study medications, body mass index > 35 kg/m2, patients with sickle cell or Reynaud diseases, and patient refusal. Patients with a history of psychiatric illness or on chronic opioids use were also excluded. In the preoperative holding area, a 20-gauge cannula was inserted in the contra-lateral side of the operated hand and intravenous (IV) infusion of Ringer lactate (5 mL/kg/h) was started. Then, patients were randomly assigned into one of 2 groups (53 patients in each group) to receive either IVRA with lidocaine plus nalbuphine (LN group) or IVRA with lidocaine only (L group). Randomization was based on computer-generated codes maintained in sequentially numbered opaque envelopes. In the operating room, patients were connected to the standard monitors, which included electrocardiograph leads II and V5, heart rate, arterial oxygen saturation (SpO2), and non-invasive blood pressure. All patients received another 20-G cannula inserted in the distal vein of the operated hand through which anesthetic drugs were given. The extremity of the operated hand was elevated and exsanguinated by tightly wrapping an Esmarch rubber bandage from distal to proximal direction, and a double pneumatic tourniquet (A. T. S® 3000 Automatic Tourniquet System, Zimmer Surgical, Inc., 200 West Ohio Ave, Dover, Ohio, USA) was placed around the upper arm. This tourniquet uses the automatic detection of limb occlusion pressure (LOP) which is the minimum pressure required to stop the arterial blood flow into the operative limb distal to the cuff. Then, the proximal cuff was inflated. To assure the proper performance of the tourniquet, the absence of radial artery pulsations and failure of pulse oximetry tracing in the ipsilateral index finger was confirmed. After the bandage was removed, patients were injected with 3 mg/kg 2% lidocaine (B. Braun Melsungen AG, D-34209 Melsungen, Germany) plus 1 mL nalbuphine (Nalbuphine hydrochloride Inj. ® 10 mg/mL, Hospira Inc., Lake Forest, IL, USA) (LN group) or 3 mg/kg 2% lidocaine plus 1 mL of 0.9% saline (L group). The volume of the study medications mixture was diluted with 0.9% saline to a total of 40 mL and was injected over 60 seconds. Study medications were prepared by an anesthesia assistant not involved in the study. Data were collected by research staff who were blinded to the study medications. The onset of the sensory block was determined by the pinprick method with a 22-G short-beveled needle every 30 seconds until loss of pain sensation. The response of the patient was tested in the dermatomal sensory distribution of the ulnar, radial, and median nerves in a random sequence. The motor block was assessed at one minute intervals until the patient was noted to produce no movement of any finger. When sensory and motor block were ensured, surgical intervention was then allowed. Ten minutes after complete sensory and motor blocks, the distal cuff was inflated and the proximal cuff was deflated. If the patient complained of pain at the surgical site, the plan of anesthesia was changed by giving additional local bupivacaine at the site of surgery or general anesthesia and the patient was excluded from the analysis. During intra-operative periods, fentanyl 1 mcg/kg was given IV if the patient complained of tourniquet pain and to maintain the visual analog scale of pain (VAS) below 30. At the end of the surgery, the distal tourniquet was deflated by repeated inflation-deflation technique (the tourniquet was deflated 3 times for 10 second periods followed by one minute of re-inflation). The distal tourniquet was not deflated before 30 minutes after local anesthetic injection and was not inflated more than 90 minutes. After tourniquet deflation, patients

were closely observed for any symptoms or signs of the injected medications' systemic toxicity or hemodynamic changes (± 15% from baseline). During the first 6 hours after tourniquet deflation, fentanyl 0.5 mcg/kg was given to keep VAS < 3. In addition, diclofenac potassium 50 mg oral tablet was given if requested by patients and/or to keep VAS below 30.

Study Measurements

Patients were instructed during the preoperative evaluation about the 100 mm VAS; in which 0 indicated no pain and 100 indicated the worst pain imaginable. The intensity of tourniquet pain and pain at the operative site was assessed using VAS. Tourniquet pain was assessed every 5 minutes from the start of inflation until complete tourniquet deflation. Pain at the operative site was assessed every 30 minutes starting after tourniquet deflation for 2 hours, then hourly for 6 hours, then every 4 hours for the rest of the first 24 hours. Onset time of sensory and motor blocks was recorded. Onset time of sensory and motor blocks was the time elapsed from the injection of the study medications to the onset of complete sensory and motor blocks, respectively. In addition, the recovery time of both sensory and motor blocks was evaluated and recorded. Sensory recovery time was the time elapsed after tourniquet deflation to the recovery of pain sensation in the operated hand as determined by the pinprick test in all dermatomal distribution of the ulnar, radial, and median nerves. Motor block recovery time was the time after tourniquet deflation to the movement of all fingers. Sedation was assessed by Ramsay sedation scores (RSS) (8) at 30-minute intervals starting from tourniquet deflation and continued for 6 hours. The number of patients requesting intraoperative fentanyl was recorded. In addition, we recorded the time to first analgesic request which was the time of the first analgesic request given to keep VAS below 30 after tourniquet inflation. Also, postoperative fentanyl and diclofenac consumption during the 24 hours was calculated. Mean arterial blood pressure and heart rate were recorded before local anesthetic injection and every 5 minutes intraoperatively. For the purpose of the study during the postoperative period, mean blood pressure, heart rate, and PONV were recorded at the same time interval of postoperative pain. Any intraoperative or postoperative adverse events were recorded and treated, such as respiratory depression (respiratory rate < 10 breaths/min), hypoxemia (SPO2 < 90%), hypotension (mean blood pressure, 15% below baseline), or bradycardia (heart rate < 50 beats/min). Other study medications side effects such as nausea, vomiting, sedation, and dizziness were recorded and treated accordingly. A subgroup of patients (10 patients in LN group and 12 in L group) was tested for cortisol levels, as a marker of stress response, before anesthetic injection and at 4 hours after skin incision.

Statistical Analysis

Statistical analysis was done using the Statistical Package for Social Science (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD, numbers, and percentages. Student's t-test was used to compare demographic data, hemodynamic parameters, sensory and motor blocks onset, and recovery times. Categorical variables were analyzed using Chi-square ($\chi 2$) test. $P < 0.05$ was considered significant. Sample size was calculated by using the World Health Organization, Geneva, sample size software, version 2.0. Based on published literature (9), the mean duration of analgesia for lidocaine was 74 ± 61 minutes. We hypothesized that the addition of nalbuphine to lidocaine would increase the analgesia time by 30%. Putting these values in the sample size software with the power of 80% and significance level of 5%, the sample size came to 48 patients in each group. For contingencies (drop-outs, incomplete data) the sample size was inflated by 10%. The final sample size came to be 53 patients in each group.

Results

The study recruited 106 adult patients who underwent unilateral hand surgery under IVRA. Figure 1 shows the study flowchart. One patient in LN group (carpal tunnel syndrome) and 3 patients in the L group (one carpal tunnel syndrome and 2 ganglions) were excluded from the study analysis because they needed a local injection of bupivacaine at the site of the surgery. Table 1 shows demographic and clinical data for both study groups. There were no significant differences regarding age, weight, gender, duration of surgery, tourniquet time, or type of hand surgery between the 2 groups. During tourniquet inflation, the study showed that the intensity of tourniquet pain was significantly lower in the LN group compared to the L group from 15 to 30 minutes following tourniquet inflation (Fig. 2). After tourniquet deflation, VAS was significantly lower in the LN group compared to the L group during the first 3 hours postoperatively (Fig. 3). Table 2 shows that the mean duration of onset time for both sensory and motor blocks was significantly

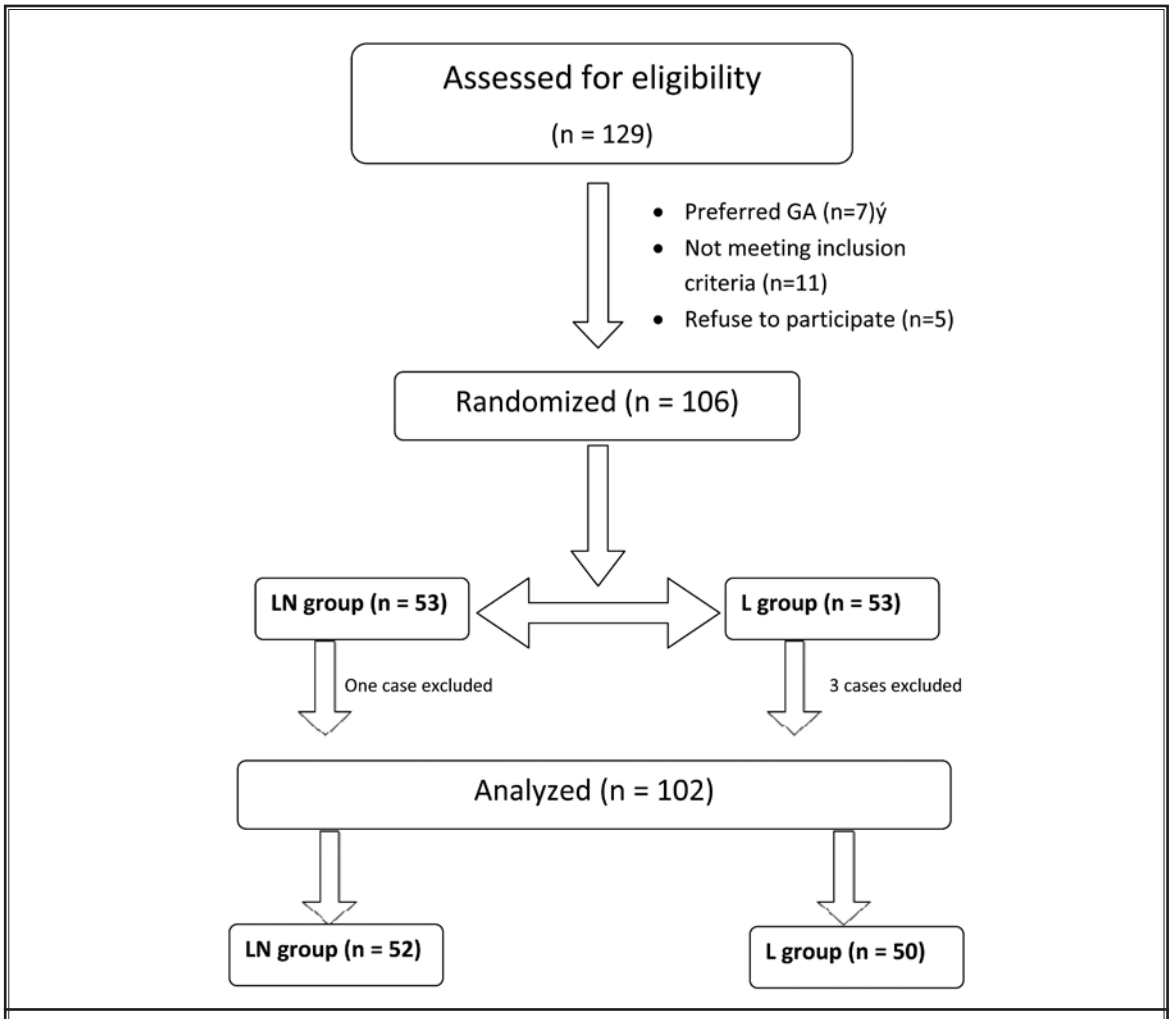

Fig. 1. *Study flow chart.*

Table 1. *Patients demographic and clinical data.*

Variable	LN group (n = 52)	L group (n = 50)
Age (y)	33.4 ± 11.3	31.1 ± 12.2
Weight (kg)	69.7 ± 9.2	71.6 ± 8.3
Gender (M/F)	23/29	19/31
Duration of surgery (min)	45 ± 11	43 ± 15
Duration of tourniquet (min)	58 ± 12	55 ± 14
Type of surgery:		
Ganglion excision (right/left)	15 (8/7)	10 (6/4)
Carpal tunnel syndrome (right/left)	15 (9/6)	18 (10/8)
Tendon release (right/left)	10 (4/6)	6 (2/4)
Trigger finger (right/left)	7 (3/4)	9 (3/6)
K-wires removal (right/left)	5 (2/3)	7 (5/2)

No significant differences ($P > 0.05$) between the 2 study groups.

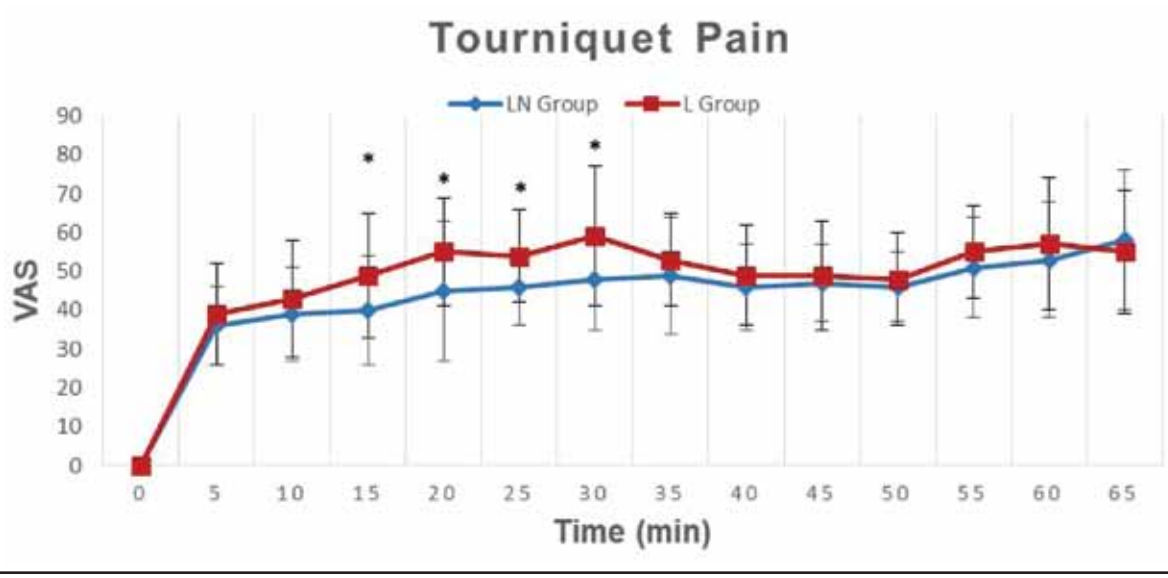

Fig. 2. *Comparison of tourniquet pain.*

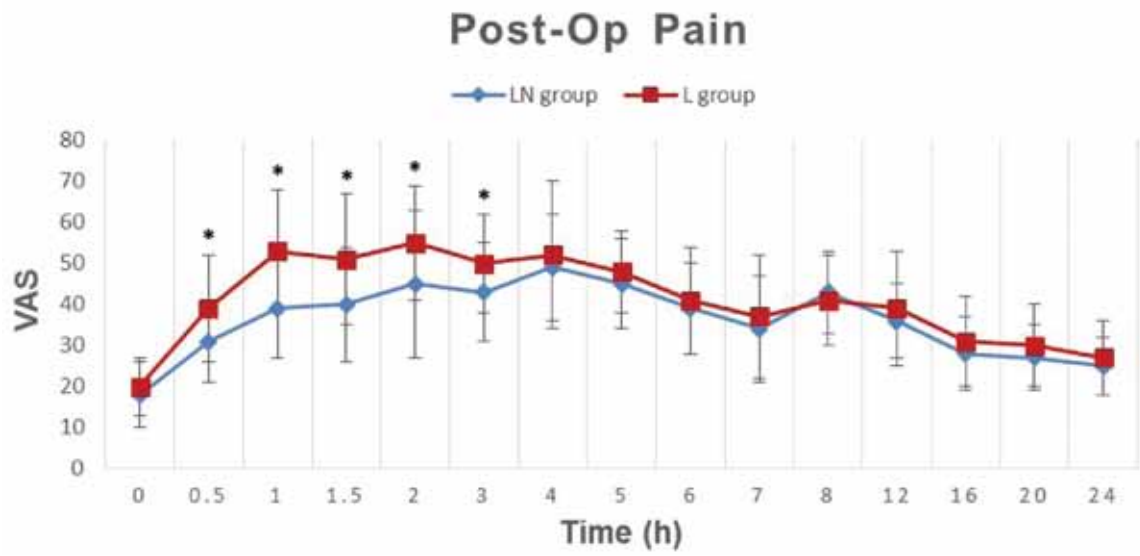

Fig. 3. *Postoperative pain scores.*

shorter in the LN group. Also, the recovery time of both sensory and motor blocks was significantly longer in the LN group. After tourniquet deflation, 7 patients in the LN group developed nausea compared to 2 patients in the L group (P = 0.16). None of the patients in either group developed vomiting during the postoperative 24 hours. During surgery and postoperatively, none of the patients had RSS of more than 2 in either group and all patients were responsive to oral commands during intra- and postoperative periods. The mean time for the first analgesic request was significantly delayed in the LN group (211 ± 62 minutes) compared to the L group

Table 2. *Onset and recovery time of sensory and motor blocks (min).*

Variable	LN group (n = 52)	L group (n = 50)	*P*-value
Sensory block onset time	3.92 ± 2.27	5.86 ± 2.13	< 0.0001
Sensory block recovery time	8.36 ± 2.12	5.93 ± 2.83	< 0.0001
Motor block onset time	5.67 ± 2.61	8.15 ± 3.87	0.0002
Motor block recovery time	7.69 ± 2.53	6.23 ± 3.58	0.017

$P < 0.05$ was considered significant.

(83 ± 37 minutes) ($P < 0.0001$). Seven patients in the LN group requested intraoperative fentanyl compared to 18 patients in the L group ($P = 0.01$). The mean dose of intraoperative fentanyl rescue was 9.4 ± 3.1 in the LN group compared to 22.3 ± 6.8 mcg in the L group ($P < 0.0001$). For postoperative fentanyl, it was 34.6 ± 15.3 in the LN group compared to 54.8 ± 18.7 mcg in the L group ($P < 0.0001$). The mean dose of diclofenac consumption during 24 hours was 24.7 ± 12.4 in the LN group compared to 28.3 ± 11.7 mg in the L group ($P = 0.13$). After tourniquet deflation, 6 patients in the LN group and 2 patients in the L group complained of dizziness which lasted a few minutes and resolved spontaneously ($P = 0.27$). During surgery and postoperatively, mean blood pressure and heart rate showed non-significant changes between the 2 groups (data not shown). None of the patients in either group showed hemodynamic instability, respiratory depression, hypoxemia, perioral paresthesia, or pruritus. The mean baseline cortisol level was 359.2 ± 93.2 in the LN group compared to 335.5 ± 105.3 ($P = 0.23$) (normal range = 138 – 635 nmol/L). At 4 hours postoperatively, it was 480.3 ± 68.5 in the LN group compared to 496.2 ± 75.8 in the L group ($P = 0.27$). All levels were within normal range.

Discussion

The study showed that the addition of nalbuphine to lidocaine for IVRA significantly reduces early tourniquet and postoperative pain intensity compared to lidocaine alone. Also, it accelerates the onset and prolongs the recovery time for both sensory and motor blocks with no significant side effects. Furthermore, the study showed that nalbuphine delays the need for postoperative analgesia and decreases the need of intraoperative and early postoperative analgesic requirements.

Nalbuphine had the longest duration of postoperative analgesia and the longest time to first analgesic rescue when compared to tramadol or lidocaine alone for IVRA. Also, it had the shortest onset time of sensory and motor blocks in contrast to lidocaine alone (5).

Due to the paucity of studies on nalbuphine for IVRA, we have reviewed the literature for other routes of its administration. Intrathecal nalbuphine, as an adjuvant to bupivacaine, has been found to prolong the duration of analgesia without increasing the incidence of side effects (10,11). However, Etches et al (12) found that epidural nalbuphine failed to provide adequate analgesia in patients undergoing thoracotomy. The lack of effectiveness of nalbuphine may be attributed to the difference in the type of surgery and route of its administration. Nalbuphine has as potent an analgesic effect as morphine, but with a better safety profile and fewer side effects such as pruritus, respiratory depression, and PONV (7). Indeed, our study showed that the side effects in the nalbuphine group were few without significant differences compared to the lidocaine group. Furthermore, epidural nalbuphine in 10 mg dose with lidocaine revealed none of the following side effects: PONV, sedation, pruritus, or respiratory depression (13). Fewer side effects of nalbuphine may be attributed to its central antagonist activity on the mu receptors. The exact mechanism of the peripheral action of nalbuphine is not well known. Different theories were postulated to explain the analgesic action of opioids in IVRA; opioids might exert their peripheral action through peripheral opioid receptors (14,15). Also, opioids may have their own local anesthetic effect by blocking sodium channels at the peripheral nerve endings (16,17). Finally, the beneficial effect of nalbuphine on postoperative pain could be related to its systemic absorption after tourniquet deflation.

The study showed non-significant changes of cortisol levels between the 2 groups. This might be explained by the small number of patients (10 patients in the LN group and 12 in the L group), short surgical duration, and less extensive surgery (18). Surgical trauma causes acute release of plasma cortisol levels with a peak value achieved within 4 to 6 hours after surgery. A reduced stress response as measured by cortisol concentration may have contributed to the enhancement of patient recovery (19,20). Opioids have been found to suppress the release of cortisol that results from surgical stimula-

tion (21). Unfortunately, there are no previous similar studies examining the effect of nalbuphine on cortisol levels. However, there is one report that found no effect of nalbuphine on cortisol levels in cocaine abusers. They believe that the mu action of nalbuphine may have blocked kappa agonist-induced stimulation of cortisol (22).

Study Limitations

The main limitation of this study was the use of a single dose of nalbuphine. Serial doses of nalbuphine need to be studied to find out the optimal dose with the lowest side effects. Finally, inclusion of a study group in which the nalbuphine given systemically could determine whether its beneficial effects were due to its local or systemic action.

Conclusions

When added to lidocaine in IVRA, nalbuphine was observed to decrease early tourniquet and early postoperative pain and delay the need for rescue analgesia. Also, it accelerates the onset and prolongs the recovery time for both sensory and motor blocks with no significant side effects. However, it has neither effect on late analgesic consumption nor postoperative cortisol levels.

References

1. Acalovschi I, Cristea T, Margarit S, Gavrus R. Tramadol added to lidocaine for intravenous regional anesthesia. *Anesth Analg* 2001; 92:209-214.
2. Jankovic RJ, Visnjic MM, Milic DJ, Stojanovic MP, Djordjevic DR, Pavlovic MS. Does the addition of ketorolac and dexamethasone to lidocaine intravenous regional anesthesia improve postoperative analgesia and tourniquet tolerance for ambulatory hand surgery? *Minerva Anestesiol* 2008; 74:521-527.
3. Kumar A, Sharma D, Datta B. Addition of ketamine or dexmedetomidine to lignocaine in intravenous regional anesthesia: A randomized controlled study. *J Anaesthesiol Clin Pharmacol* 2012; 28:501-504.
4. Abdel-Ghaffar HS, Kalefa MA, Imbaby AS. Efficacy of ketamine as an adjunct to lidocaine in intravenous regional anesthesia. *Reg Anesth Pain Med* 2014; 39:418-422.
5. Youssef MI, Elzayyat NS. Lidocaine-nalbuphine versus lidocaine-tramadol for intravenous regional anesthesia. *Ain-Shams J Anesthesiol* 2014; 7:198-204.
6. Brock-Utne JG, Ritchie P, Downing JW. A comparison of nalbuphine and pethidine for postoperative pain relief after orthopaedic surgery. *S Afr Med J* 1985; 68:391-393.
7. Zeng Z, Lu J, Shu C, Chen Y, Guo T, Wu QP, Yao SL, Yin P. A comparison of nalbuphine with morphine for analgesic effects and safety: Meta-analysis of randomized controlled trials. *Sci Rep* 2015; 5:10927.
8. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *BMJ* 1974; 2:656-659.
9. Bansal A, Gupta S, Sood D, Kathuria S, Tewari A. Bier's block using lignocaine and butorphanol. *J Anaesthesiol Clin Pharmacol* 2011; 27:465-469.
10. Culebras X, Gaggero G, Zatloukal J, Kern C, Marti RA. Advantages of intrathecal nalbuphine, compared with intrathecal morphine, after cesarean delivery: An evaluation of postoperative analgesia and adverse effects. *Anesth Analg* 2000; 91:601-605.
11. Mukherjee A, Pal A, Agrawal J, Mehrotra A, Dawar N. Intrathecal nalbuphine as an adjuvant to subarachnoid block: What is the most effective dose? *Anesth Essays Res* 2011; 5:171-175.
12. Etches RC, Sandler AN, Lawson SL. A comparison of the analgesic and respiratory effects of epidural nalbuphine or morphine in postthoracotomy patients. *Anesthesiology* 1991; 75:9-14.
13. Camann WR, Hurley RH, Gilbertson LI, Long ML, Datta S. Epidural nalbuphine for analgesia following caesarean delivery: Dose-response and effect of local anaesthetic choice. *Can J Anaesth* 1991; 38:728-732.
14. Stein C, Yassouridis A. Peripheral morphine analgesia. *Pain* 1997; 71:119-121.
15. Paus R, Schmelz M, Bíró T, Steinhoff M. Frontiers in pruritus research: Scratching the brain for more effective itch therapy. *J Clin Invest* 2006; 116:1174-1186.
16. Power I, Brown DT, Wildsmith JAW. The effect of fentanyl, meperidine and diamorphine on nerve conduction in vitro. *Reg Anesth* 1991; 16:204 -208.
17. Armstrong PJ, Morton CP, Nimmo AF. Pethidine has a local anaesthetic action on peripheral nerves in vivo. *Anaesthesia* 1993; 48:382-386.
18. Chernow B, Alexander HR, Smallridge RC, Thompson WR, Cook D, Beardsley D, Fink MP, Lake CR, Fletcher JR. Hormonal responses to graded surgical stress. *Arch Intern Med* 1987; 147:1273-1278.
19. Nicholson G, Burrin JM, Hall GM. Perioperative steroid supplementation. *Anaesthesia* 1998; 53:1091-1104.
20. Bekker A, Haile M, Kline R, Didehvar S, Babu R, Martiniuk F, Urban M. The effect of intraoperative infusion of dexmedetomidine on the quality of recovery after major spinal surgery. *J Neurosurg Anesthesiol* 2013; 25:16-24.
21. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; 85:109-117.
22. Goletiani NV, Mendelson JH, Sholar MB, Siegel AJ, Skupny A, Mello NK. Effects of nalbuphine on anterior pituitary and adrenal hormones and subjective responses in male cocaine abusers. *Pharmacol Biochem Behav* 2007; 86:667-677.