Brachial Plexus Block For Ambulatory Upper Limb Surgeries: Comparison of the Effects of Nalbuphine Versus Dexamethasone: Prospective, randomized, double-blinded, controlled clinical trial.

Mohamed Gaber Mohamed El-Sayed*, Ahmed Mohamed Salama, Ayman Abd-El Salam Hassan, Fatma Mahmoud Ahmed
Department of Anesthesia and Surgical Intensive Care, Faculty of Medicine, Zagazig University, Zagazig, Al-Sharkia Governorate, Egypt

Article History:
Received on: 10 Feb 2020
Revised on: 12 Mar 2020
Accepted on: 13 Mar 2020

Keywords:
Brachial plexus, dexamethasone, nalbuphine

ABSTRACT
Addition of an adjuvant to local anesthetics improves the quality of nerve block and reduces the need for postoperative opioids intake. The study was aimed to compare the efficiency of dexamethasone versus nalbuphine as perineural additives to local anesthetics mixture in supraclavicular brachial plexus block. The study included 45 patients scheduled for ambulatory upper extremities operations under the supraclavicular brachial plexus block. The patients were allocated to three equal groups (n=15): (i) Group C: patients received 30 mL of local anesthetics (bupivacaine 0.5% + Lidocaine 2% 1:1 mixture) + 2 ml normal saline. (ii) Group D: patients received 30 mL volume of local anesthetics (bupivacaine 0.5% + Lidocaine 2% 1:1 mixture) + 8 mg dexamethasone 0.4% (2 mL). (iii) Group N: patients received 30 mL of (bupivacaine 0.5% + Lidocaine 2% 1:1 mixture) +10 mg nalbuphine HCl (completed to 2 mL with normal saline). We compared the duration of postoperative analgesia, total opioid consumption, and complications in the first 24 hours. Statistically significant prolongation in the duration of analgesia was noticed in group D and group N with the least opioid consumption in group N. Addition of dexamethasone or nalbuphine to lidocaine/bupivacaine mixture can prolong the duration of analgesia and reduce opioids consumption after supraclavicular brachial plexus block.

*Corresponding Author
Name: Mohamed Gaber Mohamed El-Sayed
Phone: 
Email: mgaber200098@gmail.com

ISSN: 0975-7538
DOI: https://doi.org/10.26452/ijrps.v11i2.2273

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INTRODUCTION
Brachial plexus block (BPB) provides a unique alternative option for anesthesia and analgesia of upper limb's surgeries. It helps to optimize postoperative pain relief and decrease the annoying symptoms associated with general anesthesia such as nausea, sore throat, and vomiting and so help reduce the hospital stay (Perlas et al., 2009).

Kulenkampff and Persy were the first to describe the supraclavicular approach to the brachial plexus in the early 20th century. This technique of brachial plexus block can provide excellent regional anesthesia to the upper extremity than other approaches. It is so named the spinal of the upper limb. It requires the needle to be directed to the first rib where the divisions of brachial plexus are in close relation with the subclavian artery (Arcand et al., 2005).

Recently, ultrasonography guidance helped to decrease the incidence of pneumothorax and vascular puncture, which were common with the classic landmark technique of this approach. Ultrasonogra-
Phy guidance provides real-time visualization of the needle pathway during the procedure (Karmakar, 2017).

The use of local anesthetics solely for BPB provide applicable surgical anesthesia but still have a quite brief period of postoperative analgesia. So, different additives such as clonidine, magnesium, and midazolam (Kaur et al., 2013; Dogru et al., 2013; Jarbo et al., 2005) have been used besides local anesthetics to obtain dense, quick, and extended analgesia; however, the results are either unsatisfactory or associated with side effects (Das et al., 2017).

Nalbuphine is considered an antagonist-agonist opioid with an antagonistic activity on μ (mu) opioid receptors and agonistic activity on κ (kappa) receptors with an analgesic effect parallel to morphine whereas its antagonistic effect is almost 1/3rd that of naloxone. Nalbuphine has a better safety profile than morphine, characterized by stable hemodynamics and a ceiling effect on respiratory depression. Addition of nalbuphine hydrochloride to brachial plexus block has shown the potentiality to improve the quality of postoperative analgesia (Gupta et al., 2016). Dexamethasone has shown to augment the duration of postoperative analgesia when given as an adjunct for peripheral nerve blocks. This effect could be attributed to the anti-inflammatory action of dexamethasone or the possible suppression of neural signals transmission in nociceptive C-fibers (Huynh et al., 2015).

**PATIENTS AND METHODS**

This prospective, randomized, controlled clinical study was performed in Zagazig University Hospitals from November 2018 to December 2019, after obtaining approval from the Institutional Research Board (IRB) and the Ethical Committee (clinical trial registration ID: NCT04194320). The details of the procedure were explained to the patients and then informed consent was taken after their acceptance to participate. A total of 45 patients scheduled for ambulatory upper extremities operations beneath the shoulder level were involved in the study. Patients included were aged between 21 and 60 years, with BMI below 30 kg/m² and classified by the American Society of Anesthesiologists (ASA) for physical condition assessment as Class I–II. Patients with pathological coagulopathy, peripheral neuropathy, infection at the injection site or allergy to lidocaine, bupivacaine, dexamethasone or nalbuphine were excluded from the study.

Visual analogue scale (VAS) with ten centimeters grades (0 – no pain and 10 – worst pain imaginable) was explained during the preoperative visit. Intravenous access was secured and supplemental oxygen was provided at 4 L/min via nasal cannula. Procedural sedation had been administered intravenously by midazolam 0.01 to 0.1 mg/kg (Butterworth et al., 2013). Inside the operating theater, standard ASA monitors such as electrocardiogram, non-invasive blood pressure, and peripheral O₂ saturation monitors were connected to the patient and baseline readings were listed. All equipment for general anesthesia and resuscitation were already prepared.

Then, the patients were allocated at random to three groups of equal populations using computer-generated tables, each containing 15 patients:

1. Group C (n=15), patients received 30 mL of local anesthetics (bupivacaine 0.5% + Lidocaine 2% 1:1 mixture) + 2 ml normal saline.
2. Group D (n=15), patients received 30 mL of local anesthetics (bupivacaine 0.5% + Lidocaine 2% 1:1 mixture) + 8 mg dexamethasone 0.4% (2 mL).
3. Group N (n=15), patients received 30 mL of (bupivacaine 0.5% + Lidocaine 2% 1:1 mixture) + 10 mg nalbuphine HCl (completed to 2 mL with normal saline).

Supraclavicular BPB was performed using an 8 to 12 MHz linear ultrasound probe (Mindray M5-Shenzhen MindrayBiomedical electronics co., LTD) placed in a sterile sheath and using the in-plane technique. The patients were kept comfortably supine while the head was tilted towards the opposite side to be blocked and after identifying the brachial plexus near the first rib (Figure 1), anterolateral to the subclavian artery, skin topicalization was done with lidocaine 1% then a 22-gauge 50 mm sterile blunt needle Stimuplex (B. Braun, Melsungen, AG) was directed towards the angle made by the first rib, BPB, and subclavian artery (Fig.1). After ensuring negative aspiration, a local anesthetic mixture of “32 ml” was injected in 5-mL aliquots.

Primary outcome parameters were the duration of analgesia and the total fentanyl consumption in the first 24 hours postoperative. Secondary outcome measures included the onset time and duration of both motor and sensory blocks and any associated side effects such as nausea, pruritus, vomiting, and sedation.

Patients were assessed for onset of sensory and motor blocks at every 2 minutes interval until the
desired surgical anesthesia was achieved with "time 0" being the time of completion of the injection. The onset of sensory block was determined from the end of injection of the local anesthetic mixture to loss of pinprick sensation in the median, radial, ulnar, and musculocutaneous nerve distributions. Pinprick test was done using sterile 25G needle. The onset of motor block was determined from the completion of injection of the local anesthetic mixture to the loss of flexion and extension movement in elbow, wrist, and fingers.

The analgesia time was assigned as the period from the start of sensory block to the first complaint of pain at the wound that had VAS ≥ 4. Motor block period was defined as the duration from the start of a motor block to the recovery of the wrist or hand mobility. It was specified by asking the patients to note the exact time when they could first move the fingers of the blocked limb. Perioperative heart rate, respiratory rate, non-invasive blood pressure, and oxygen saturation had been monitored initially and throughout the surgery. Any associated complications such as nausea, vomiting, sedation, and pruritis were recorded. Postoperative pain was assessed at 1-hour interval for the first 8 hours, then every 4 hours till the 24 postoperative hours. When analgesia was in demand (VAS ≥ 4), injection of fentanyl 25 μg increments were given intravenously as needed up to 200 μg/hour. The total dose of fentanyl consumption in the first 24 hours was estimated for analysis.

Statistical analysis

The recorded data were computerized and analyzed using Statistical Package of Social Services version 22 (SPSS). Continuous Quantitative data, e.g. weights were displayed using the mean ± SD, and categorical qualitative data were displayed using absolute numbers & percentage. Suitable statistical tests of significance were used after checking for normality. The results were considered statistically significant when the significant probability was less than 0.05 (P < 0.05).

RESULTS

Sixty patients (60) had been enrolled in this trial, 15 of them were precluded from the study due to failure to attain a complete surgical anesthesia within 30 minutes and the surgery was accomplished under general anesthesia (Figure 2). All groups were comparable regarding their demographic data, including age, height, weight, gender, BMI, ASA grade, and surgery time (Table 1). Perioperative hemodynamics, heart rate, non-invasive blood pressure, oxygen saturation, and respiratory rate were also comparable in the study groups.

Figure 1: Ultrasound image showing the needle "yellow arrows" directed to the angle in between the first rib and the subclavian artery "SA".

Figure 2: Consort flow chart

Regarding the onset time for both sensory and motor blocks, there was no significant difference among the three groups. Still, there was a high statistical difference among the groups regarding the motor and sensory block duration where both were more extended in dexamethasone and nalbuphine than the control group, with no statistically significant difference between nalbuphine and dexamethasone groups (Table 2).

The postoperative analgesia was significantly longer in nalbuphine group than in dexamethasone and control groups (825.47 ± 62.47 vs 796.2 ± 23.41, and 517.5 ± 21.49 minutes, respectively) with no statistically significant difference between nalbuphine and dexamethasone groups. The total fentanyl consumption and visual analogue score for the first 24 hours postoperative were statistically lower in group N with no statistically significant complications among the studied groups.
Table 1: Demographic features of the studied groups

| Item                        | Group C (N=15) | Group D (N=15) | Group N (N=15) | χ² /KWt | P-value |
|-----------------------------|----------------|----------------|----------------|---------|---------|
| Age (years)                 |                |                |                |         |         |
| Mean ± SD                   | 41.53 ± 11.92  | 36.80 ± 9.93   | 38.73 ± 12.73  | 1.32    | 0.515(NS)|
| Sex                         |                |                |                |         |         |
| Male/Female                 | 10/5           | 9/6            | 10/5           | 0.207   | 0.901(NS)|
| Weight (kg)                 |                |                |                |         |         |
| Mean ± SD                   | 84.87 ± 7.42   | 82.67 ± 7.33   | 81.07 ± 7.98   | 1.40    | 0.495(NS)|
| Height (cm)                 |                |                |                |         |         |
| Mean ± SD                   | 172.26 ± 5.9   | 174.6 ± 8.4    | 173.2 ± 7.57   | 1.15    | 0.561(NS)|
| BMI (kg/m²)                 |                |                |                |         |         |
| Mean ± SD                   | 28.54 ± 0.99   | 27.16 ± 2.04   | 27.01 ± 1.67   | 8.73    | 0.013(NS)|
| ASA Grade I / II            |                |                |                |         |         |
| Onset time for sensory block (minutes) |          |                |                |         |         |
| Mean ± SD                   | 9.56 ± 1.01    | 9.43 ± 1.62    | 9.16 ± 1.27    | 1.03    | 0.592(NS)|
| Duration of sensory block (minutes) |          |                |                |         |         |
| Mean ± SD                   | 457.2 ± 19.48  | 676.6 ± 26.44  | 701.6 ± 40.5   | 30.20   | 0.000*(HS)|
| Onset time for motor block (minutes) |          |                |                |         |         |
| Mean ± SD                   | 12.57 ± 1.67   | 13.10 ± 1.51   | 12.0 ± 1.26    | 3.89    | 0.142(NS)|
| Duration of motor block (minutes) |          |                |                |         |         |
| Mean ± SD                   | 390.6 ± 9.78   | 496.93 ± 33.27 | 516.7 ± 23.6   | 30.21   | 0.000*(HS)|
| Duration of postoperative analgesia (minutes) |          |                |                |         |         |
| Mean ± SD                   | 517.5 ± 21.49  | 796.2 ± 23.41  | 825.47 ± 62.47 | 30.31   | 0.000*(HS)|
| p-value of MWt              | ---            | 0.000*         | 0.000*         |         |         |
| Total fentanyl dose in the first 24 hours "µg" |          |                |                |         |         |
| Mean ± SD                   | 153.33 ± 32.55 | 63.33 ± 15.99  | 35 ± 12.67     | 36.76   | 0.000*(HS)|
| p-value of MWt              | ---            | 0.000*         | 0.000*         |         |         |

χ²: chi-square test KWT: Kruskal Wallis test. P<0.05 is significant. NS: Not significant

Table 2: BPB characteristics among the studied groups

| Item                        | Group C (N=15) | Group D (N=15) | Group N (N=15) | KWT   | P-value |
|-----------------------------|----------------|----------------|----------------|-------|---------|
| Onset time for sensory block (minutes) |          |                |                |       |         |
| Mean ± SD                   | 9.56 ± 1.01   | 9.43 ± 1.62    | 9.16 ± 1.27    | 1.03  | 0.592(NS)|
| Duration of sensory block (minutes) |          |                |                |       |         |
| Mean ± SD                   | 457.2 ± 19.48 | 676.6 ± 26.44  | 701.6 ± 40.5   | 30.20 | 0.000*(HS)|
| Onset time for motor block (minutes) |          |                |                |       |         |
| Mean ± SD                   | 12.57 ± 1.67  | 13.10 ± 1.51   | 12.0 ± 1.26    | 3.89  | 0.142(NS)|
| Duration of motor block (minutes) |          |                |                |       |         |
| Mean ± SD                   | 390.6 ± 9.78  | 496.93 ± 33.27 | 516.7 ± 23.6   | 30.21 | 0.000*(HS)|
| Duration of postoperative analgesia (minutes) |          |                |                |       |         |
| Mean ± SD                   | 517.5 ± 21.49 | 796.2 ± 23.41  | 825.47 ± 62.47 | 30.31 | 0.000*(HS)|
| p-value of MWt              | ---           | 0.000*         | 0.000*         |       |         |
| Total fentanyl dose in the first 24 hours "µg" |          |                |                |       |         |
| Mean ± SD                   | 153.33 ± 32.55| 63.33 ± 15.99  | 35 ± 12.67     | 36.76 | 0.000*(HS)|
| p-value of MWt              | ---           | 0.000*         | 0.000*         |       |         |

KWt: Kruskal Wallis test to compare between 3 groups MWt: Mann Whitney test to compare between 2 groups
a: comparison between control and dexamethasone group; comparison between control and nalbuphine group
b: comparison between nalbuphine and dexamethasone group
*P < 0.05 is significant.
*NS: non-significant. *HS: highly-significant
DISCUSSION

Local anesthetics alone for BPB provide excellent surgical anesthesia but still have short-lived postoperative analgesia. This study was done to compare the efficacy of adding dexamethasone or nalbuphine to lidocaine/bupivacaine mixture for the supraclavicular approach of brachial plexus block regarding the beginning and duration of both motor and sensory blocks, postoperative analgesia period, and total opioid consumption in the first 24 hours postoperative.

Regarding the onset of sensory and motor blocks, our study showed that there was no significant statistical difference among the groups. These results are in agreement with the results of Gupta et al. (2016) and Das et al. (2017) in their studies on nalbuphine as an adjuvant to 0.5% bupivacaine in BPB. Also, these results are in agreement with the results of Parrington et al. (2010) in their study on dexamethasone as an adjuvant to mepivacaine in supraclavicular BPB.

However, Jain and Nazir (2017) and Konkyana et al. (2018) in their studies evaluating the nalbuphine as an additive to bupivacaine in BPB found that nalbuphine significantly shortened the onset of sensory and motor blocks. Biradar et al. (2013) showed that the onset of both motor and sensory blocks was shorter in the dexamethasone group in their comparative study of adding dexamethasone to 1.5% lidocaine in BPB.

Our results regarding the duration of sensory and motor blocks of the dexamethasone group are in alignment with the meta-analysis done by Huynh et al. (2015) to evaluate the effect of combining dexamethasone with a local anesthetic on peripheral nerve blocks in adults. Regarding our results of the duration of sensory and motor blocks of the nalbuphine group, Gupta et al. (2016) and Das et al. (2017) in their studies on nalbuphine as an additive to bupivacaine 0.5% in BPB gave nearly the same result. This also occurred with Jain and Nazir (2017) and Konkyana et al. (2018); Abdelhaq and Elramely (2016) too found the same result but with a larger dose of nalbuphine “20 mg” than our study’s dose of “10 mg”.

The mechanism of dexamethasone action in prolonging the duration of neuronal block is not yet understood and is thought to be related to various factors. Possible explanations may be due to some sort of vasoconstriction which could decrease the absorption of local anesthetics, and suppression of the synthesis and release of the inflammatory mediators which could inhibit the transmission of nociceptive signals in the unmyelinated C-fibers (Lee et al., 2016). In view of the first time for the patients’ request for rescue analgesia, our study revealed that the analgesia time was extended in the nalbuphine and dexamethasone groups than in the control group. This was in line with the findings of Gupta et al. (2016) and Das et al. (2017) & Biradar et al. (2013) Worth to mention that there was no significant statistical difference between the dexamethasone and nalbuphine groups concerning the postoperative analgesia period.

However, there was a significant difference between the three groups regarding the total fentanyl consumption & VAS scores in the first 24 hours postoperative. The results of our study showed that the total dose of fentanyl consumed & VAS scores in the first 24 hours postoperative were far less in the nalbuphine group than the other two groups.

The mechanism of the analgesic effect of perineural nalbuphine is not yet clear. There are different theories which explain this effect and they include the possible presence of peripheral opioid receptors allowing for the analgesic effects of opioids (Stein, 2003), opioids might produce their local anesthetic action via possible sodium channels blocking the effect at the peripheral nerve endings (Likar et al., 2001), and the action of perineural nalbuphine on extending the analgesia postoperatively can be attributed to possible systemic absorption (Sehgal et al., 2011).

CONCLUSION

From the results of our study, we can conclude that the addition of 10 mg of nalbuphine hydrochloride or 8 mg of dexamethasone to (bupivacaine 0.5% + Lidocaine 2% 1:1 mixture) BPB has the advantages of prolonging the duration of the sensory block and postoperative analgesia and reduces postoperative opioids requirements without significant hemodynamic instability, with the best result regarding the quality of postoperative analgesia in the nalbuphine group.

Limitations

The limitations of our study were that we did not measure the patients’ nalbuphine or dexamethasone blood levels. This hampered the possibility of our study to assess whether the effect of both on the duration of analgesia following BPB was due to local or systemic action.

Conflict of Interests

The authors declare no conflict of interest.
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