Fentanyl and clonidine as adjuncts to a mixture of local anesthetics in potentiating postoperative analgesia in supraclavicular block: A randomized controlled study

Anisha Puri, Gurchand Singh¹, Anita Madan²

ABSTRACT

Background: Brachial plexus block is popular for upper limb surgeries as it is effective for postoperative analgesia.

Aims: The aim of the study was to compare fentanyl and clonidine as adjuncts to a mixture of local anesthetics in potentiating postoperative analgesia in the supraclavicular block.

Materials and Methods: Sixty patients of the American Society of Anesthesiologist I and II undergoing upper limb surgeries lasting more than 30 min were included and randomly divided into two groups of 30 each. In clonidine (C) group, patients received 10 ml of 0.5% bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200,000) and 1 µg/kg clonidine diluted till 35 cc with normal saline. In fentanyl (F) group, patients received 10 ml of 0.5% bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200,000) and 1 µg/kg fentanyl diluted till 35 cc with normal saline. Patients were observed for onset and duration of sensory and motor blockade, duration of analgesia, postoperative pain, and adverse effects.

Results: The mean onset of sensory block was faster in Group F (8.43 ± 2.897 min) as compared to 13.17 ± 2.451 min in Group C. The difference between the two groups was statistically strongly significant (P < 0.0001). There was a significant reduction in the onset of motor block in Group F (14.67 ± 1.84 min) compared to (18.17 ± 2.45 min) Group C with P < 0.0001 (statistically strongly significant). There was a significant increase in the duration of analgesia in Group C (16.63 ± 2.04 h) compared to Group F (8.79 ± 1.50 h) with P < 0.0001. There was bradycardia (pulse did not fall below 60) in two patients of Group C (treated with atropine intravenous [i.v.]). Two patients of Group F complained of nausea and vomiting once in the early hours of surgery for which ondansetron i.v. was given. There were no significant side effects in either of the groups.

Conclusion: Both clonidine and fentanyl establish a good safety profile. Fentanyl ensures a faster onset of sensory and motor blockade, while clonidine ensures a longer duration of sensory and motor blockade as well as prolonged analgesia.

Key Words: Clonidine, fentanyl, local anesthetics, supraclavicular block

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Puri A, Singh G, Madan A. Fentanyl and clonidine as adjuncts to a mixture of local anesthetics in potentiating postoperative analgesia in supraclavicular block: A randomized controlled study. Int J Crit Illn Inj Sci 2020;10:163-9.

Received: 16.08.2019; Revision: 23.10.2019; Accepted: 24.02.2020; Published: 29.12.2020.
INTRODUCTION

Upper limb orthopedic surgeries are preferably done under regional anesthesia nowadays.\(^1\) Regional anesthesia is safer and allows a better surgical field. It has minimal systemic and hemodynamic involvement, decreased incidence of postoperative nausea and vomiting, and better analgesia both intraoperatively and postoperatively. Regional anesthesia fastens the ambulation and discharge of the patient.\(^2,3\) Thus, regional anesthesia is preferred over general anesthesia wherever it is possible. Supraclavicular brachial plexus block for the upper limb is comparable with spinal anesthesia of the lower limb.\(^4\) It is due to the fact that it is given lateral to the subclavian artery on the first rib, below the clavicle where the nerve fibers of brachial plexus are compactly placed.\(^3\) The duration of intra- and postoperative analgesia is dependent on the local anesthetic used.\(^5\)

Local anesthetics can interrupt the transmission of the action potential of excitable membranes by binding to receptors in the Na\(^+\) channels. Lignocaine has a quick action but only till 1–1.5 h. It causes vasodilatation which is antagonized by adding a vasoconstrictor. Adrenaline added to lignocaine delays absorption and prolongs the action by delaying absorption. On the other hand, bupivacaine has a slow onset, but it prolongs the duration of analgesia. However, bupivacaine is cardiotoxic hence can be disastrous in patients in supraclavicular block where major vessels are very closely placed to the brachial plexus.\(^1,2\) Hence, combining lignocaine and bupivacaine is better than using an individual drug, as it combines the better qualities of both the drugs and side effects can be avoided. Large volumes of local anesthetics required to produce desirable effects may result in systemic side effects.\(^6\)

Local anesthetics can provide analgesia up to 4–8 h.\(^7\) Hence, they are of limited use in patients where we want to provide postoperative analgesia and short analgesia duration postoperatively is the biggest problem in upper limb surgeries.\(^8\) Hence, the use of adjuvant to increase the duration of supraclavicular brachial plexus block and decrease the dose of local anesthetics is a better and safer option to prolong analgesia.\(^9\) Various adjuvants available include epinephrine, dexamethasone, magnesium sulfate, morphine, tramadol, midazolam, ketamine, neostigmine, fentanyl, and clonidine.\(^1\)\(^,\)\(^2\)\(^,\)\(^4\)

Increase in the duration of motor and sensory block was observed on the addition of clonidine and fentanyl with local anesthetics in various clinical trials.\(^13\)\(^-\)\(^14\) Very little literature is available about the comparison between alpha-2 agonist and opioid as adjuncts to local anesthetic agents in brachial plexus block.\(^15\)\(^-\)\(^16\) Hence, we compared clonidine and fentanyl in a dose of 1 μg/kg each as adjuncts to local anesthetic agents for the enhancement of supraclavicular nerve block for upper limb surgery.

MATERIALS AND METHODS

It was a randomized, double-blind study conducted at a tertiary care hospital after obtaining consent of the ethical committee. Sixty adult patients of the American Society of Anesthesiologist (ASA) Class I and II weighing 40–70 kg of either sex, belonging to 25–60 years of age, and undergoing upper limb surgeries lasting more than 30 min were included and divided into two groups of 30 each using numbers generated by the computer randomly. Preparation of local anesthetic mixture with adjunct drugs and labeling of drugs by random number generated by computer was done by anesthetists not involved in the procedure of block or data collection. In the clonidine group (Group C), patients received 10 ml of 0.5% bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200,000) and 1 μg/kg clonidine diluted up to 35 cc with normal saline. In fentanyl group (Group F), patients received 10 ml of 0.5% bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200,000) and 1 μg/kg fentanyl diluted up to 35 cc with normal saline. We excluded diabetics, hypertensives, and patients with nephrology or hepatic disorder and pregnant patients. The sample size was calculated using 0.05 as alpha level and 0.90 beta level from data of earlier studies to obtain the required power of 0.80.\(^17\)

After obtaining informed written consent from the patient for participation and publishing of de-identified aggregate data, an intravenous (i.v.) line was secured with 18 G cannula and infusion was started with ringer’s lactate i.v. Baseline blood pressure, heart rate, respiratory rate, and SpO\(_2\) were noted. We did not take surrogate consent or include patients in our study where surrogate consent was needed. In the operation theater, all routine monitors such as noninvasive blood pressure, pulse oximetry, and electrocardiogram were attached and all vitals mentioned above were once again recorded. Ondansetron 4 mg i.v. was given as premedication.

The patient was placed in the supine position with the head turned away from the side to be blocked. The arm to be anesthetized was adducted, and the hand was extended along the side toward the ipsilateral knee as far as possible. Using the classic technique approach, the midpoint of the clavicle was identified and marked. The posterior border of the sternocleidomastoid was palpated easily when the patient raised the head slightly. Palpating the belly of the anterior scalene muscle moving toward the interscalene groove with the fingers, a mark was made at approximately 1.5–2.0 cm posterior to the midpoint of the clavicle. By palpating the subclavian artery at this site, landmark was confirmed. The area was cleaned with povidone-iodine solution. The area was then draped properly. After appropriate preparation and injection of a skin wheal, 24-G needle was inserted at the point of entry above the midpoint of the clavicle...
in the backward–inward–downward direction. Although the direction of the needle was toward the first rib, it was not always necessary to touch the rib. Paresthesia in the forearm or hand was elicited. Thirty-five milliliter of the local anesthetic solution with clonidine or fentanyl as an adjunct was injected after negative aspiration for air or blood followed by a 2 min massage to provide an even distribution of the drug. After injection of the mixture of drugs prepared, we noted the time of injection of drugs in supraclavicular brachial plexus block, time of onset of sensory and motor block, duration of sensory and motor block, and duration of analgesia.

The onset of sensory blockade was monitored every minute for the first 15 min then every 5 min till 30 min and then every 15 min till complete surgical anesthesia.

Motor blockade was assessed by the technique described by modified Bromage on the 3-point scale. It was assessed 5 min till 30 min and then every 15 min till complete motor blockade. The duration of motor block was assessed every 1 h, till the ability to move fingers only.

Statistical methods
A descriptive statistical analysis was carried out. Data were collected, tabulated, coded, and analyzed using SPSS for windows version 16.0 (SPSS Inc., Chicago, USA).

The results obtained on continuous measurements were presented in mean ± standard deviation (minimum–maximum) and the results on categorical measurements were presented in number (%). Student’s t-test (two tailed, independent) was used to find the significance of study parameters on a continuous scale between the two groups. P < 0.05 was considered statistically significant.

RESULTS

In the present study, both the groups were comparable in the demographic data with respect to age, gender, weight, and ASA grade. The duration of surgery was also comparable among the two groups.

The mean onset of sensory block was faster in Group F than in Group C.

There was a significant reduction in the onset of motor block in Group F compared to Group C.

The duration of sensory blockade was found to be longer in the clonidine group compared to fentanyl.

The duration of motor block was longer in the clonidine group compared to fentanyl group and was found to be clinically and statistically strongly significant.

In the present study, there was a significant prolongation of the duration of analgesia in Group C compared to Group F.

DISCUSSION

Upper limb trauma has become a common injury in the modern scenario, especially with growing agricultural dependency on machines. Hence, regional nerve blocks are a boon in today’s world. They can be given in full stomach patients and without any risk of drug interactions. General anaesthesia may lead to haemodynamic responses like hypertension, arrhythmias, tachycardia, wound dehiscence, increased intraocular and intracranial pressure that are avoided in regional brachial plexus block. The cost factor is also less with a regional block. Another advantage of using regional anesthesia is postoperative analgesia that can be prolonged by the addition of an adjuvant. This helps in decreasing psychological effects that may cause anxiety and distress which may cause autonomic symptoms of nausea and sweating. There is less risk of deep-vein thrombosis and chest infections in pain-free patients. Adjuvants such as dexmedetomidine, adrenaline, neostigmine, midazolam, magnesium sulfate, clonidine, and steroids and opioids including morphine, fentanyl, and tramadol are used in peripheral nerve blocks for the improvement of quality and duration of block avoiding the higher and toxic dose of individual local anesthetic.

Anesthesia of entire upper extremity and perioperative analgesia are provided by supraclavicular brachial plexus block in an easy way without any systemic side effects. While catheter-based techniques allow for sustained pain management during the peri-operative period, they can present challenges related to patient management, catheter displacement, and increased infection risk. Hence, using adjuvant to local anesthetics is a better and safer option to prolong the analgesia. Alpha-2 agonists have analgesic, anxiolytic, sedative, and sympatholytic properties, which make it a better choice for local anesthetic. The addition of clonidine or fentanyl to local anesthetics produces analgesia, sedation with minimal side effects. Their use is established as onset is rapid with prolonged analgesia.

In our study, we compared 10 ml of 0.5% bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200,000) and 1 µg/kg Clonidine diluted up to 35 cc with normal saline versus 10 ml of 0.5% bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200,000) and 1 µg/kg fentanyl diluted up to 35 cc with normal saline as taken by Rustagi et al. We took a dose of 1 µg/kg of fentanyl as was taken by a study by Paluvad and Manne. We took a dose of 1 µg/kg of clonidine as was taken by a study by Patil and Singh.
Puri, et al.: A comparative study between fentanyl and clonidine as adjuvants to a mixture of local anaesthetics in potentiating postoperative analgesia in supraclavicular brachial plexus block

The demographic data in terms of age, weight, and duration of surgery were comparable in both the groups in our study [Table 1].

Brachial plexus block is suitable to patients of all age groups, as shown by Bhattarai et al. in their study on brachial plexus block comprising patients of ages ranging between 2.6 and 90 years. However, in our study, we included patients of age group 25–60 years as difficulty in obtaining cooperation for regional blocks in children has made regional anesthesia an uncommon sole anesthetic technique, although it has been considered ideal for surgical procedures in the upper limbs.[24]

The mean onset of sensory block was faster in Group F (8.43 ± 2.89 min) as compared to Group C (13.17 ± 2.45 min) [Table 2] and the onset time of motor block was also faster (14.67 ± 1.84 min) in Group F than in Group C (18.17 ± 2.45 min) [Table 3] which was found to be strongly significant clinically and statistically (P < 0.001). Our results were in accordance with the study done by Ahmed who observed that the addition of fentanyl to a mixture of local anesthetics produced rapid onset of sensory (8.9 ± 2.9 min) and motor block (8.3 ± 2.7 min) compared to clonidine (sensory being 11.9 ± 2.7 min; motor being 9.8 ± 2.1 min) added as an adjuvant in brachial plexus.[25]

Pöpping et al. used clonidine doses ranging from 90 to 150 μg in brachial plexus block and found the onset time of sensory block of clonidine to be 12.8 ± 1.84 min.[17] The values and the results are in concurrence with our study.

Our study also correlates with the study done by Jafa et al. who found that the addition of 75 μg fentanyl into the supraclavicular brachial plexus block shortened the onset time of block (10.2 ± 1.15 min) and time to achieve complete block (21.8 ± 4.6 min).[26] Moharari et al. showed that the combination of 75 μg fentanyl and 1.5% lidocaine solution accelerated the onset of sensory and motor blockade during interscalene block.[27] Regarding the possible mechanisms for accelerating the onset of sensory and motor blockade by fentanyl in this study, they suggested that fentanyl might block the nerve conduction in the spinal roots. It means that the action of opioids injected into the perineural sheath may be more central due to diffusion or the axonal transport into epidural and subarachnoid spaces.

The mean duration of sensory block in our study was longer in Group C (10.83 ± 1.08 h) as compared to 5.66 ± 1.82 h in Group F [Table 4]. The duration of motor block in our study was also found to be longer (9.10 ± 1.06 h) in Group C than (4.40 ± 0.63 h) in Group F [Table 5], and the difference between the two groups was found to be statistically and clinically significant (P < 0.001).

Our study was also in accordance with the study done by Ahmed, who also found that the clonidine group showed longer duration of sensory (558 ± 66.4 min) and motor block (574.3 ± 40.9 min) compared with the fentanyl group where the duration of sensory block was 364.5 ± 33.3 min and duration of motor block was 388.2 ± 34.8 min.[25]

Our study showed sensory blockade for a longer duration than a motor block which is similar to a study by de Jong and Wagman[25] This is due to the fact that small fibers need less concentration of local anesthetic than large fibers. Large motor fibers require greater concentration of minimal effective concentration of local anesthetic than the small one (sensory fibers). Hence, sensory blockade is longer than the motor block and pain is felt only after the return of motor function.

The duration of analgesia was the time between the onset of action and first complaint of pain (Visual Analog Scale more than or equal to 4) and patients received the first dose of rescue analgesic. The mean duration of analgesia [Table 6] was longer in the clonidine group (16.63 ± 2.04 h) compared to the fentanyl group (8.79 ± 1.50 h) and was statistically strongly significant. A study conducted by Ahmed also found that the duration of analgesia was longer in the clonidine group (14.4 ± 1.3 h) compared to the fentanyl group (10.9 ± 1.5 h) which was in accordance with our study.[25] Specific peripheral effects of clonidine are less because alpha-2 adrenoreceptors are not present on the axon of a normal peripheral nerve. The action of clonidine in peripheral nerve blocks may be explained by four mechanisms. They include direct peripheral nerve action, anti-inflammatory effect, analgesia that is centrally mediated vasoconstriction due to alpha-2

| Parameters                  | Group-C (n = 30)          | Group-F (n = 30)          | Significance (P) |
|-----------------------------|---------------------------|---------------------------|------------------|
| Age (years)                 | 36.40 ± 9.39              | 38.53 ± 10.86             | 0.661 (NS)       |
| Sex (male/female), n (%)    | 20 (66.6)/10 (33.3)       | 19 (63.3)/11 (36.6)       | NS               |
| Weight (kg)                 | 57.90 ± 7.38              | 55.27 ± 9.14              | 0.345 (NS)       |
| Time duration of surgery (min) | 78.83 ± 30.58          | 81.50 ± 19.17             | 0.667 (NS)       |
| ASA grade, n (%)            |                           |                           |                  |
| I                           | 17 (56.6)                 | 13 (43.4)                 | NS               |
| II                          | 18 (60.0)                 | 12 (40.0)                 |                  |

NS: Not significant, ASA: American Society of Anesthesiologist
Table 2: Onset of sensory block (minutes)

| Onset       | Group-C (n = 30) | Group-F (n = 30) | Significance (P) |
|-------------|------------------|------------------|------------------|
| Sensory block | 13.17 ± 2.45     | 8.43 ± 2.89     | <0.0008 (strongly significant) |

Table 3: Onset of motor block (minutes)

| Onset       | Group-C (n = 30) | Group-F (n = 30) | Significance (P) |
|-------------|------------------|------------------|------------------|
| Motor block | 18.17 ± 2.45     | 14.67 ± 1.84     | 0.0002 (strongly significant) |

Table 4: Duration of sensory block (hours)

| Duration (hours) | Group-C (n = 30) | Group-F (n = 30) | Significance (P) |
|------------------|------------------|------------------|------------------|
| Sensory block    | 10.83 ± 1.08     | 5.66 ± 1.82      | 0.0001 (strongly significant) |

Table 5: Duration of motor block (hours)

| Duration (hours) | Group-C (n = 30) | Group-F (n = 30) | Significance |
|------------------|------------------|------------------|--------------|
| Motor block      | 9.10 ± 1.06      | 4.40 ± 0.63      | 0.0009       |

Table 6: Duration of analgesia (hours)

| Duration (hours) | Group-C (n = 30) | Group-F (n = 30) | Significance (P) |
|------------------|------------------|------------------|------------------|
| Analgesia        | 16.63 ± 2.04     | 8.79 ± 1.50      | 0.0001 (strongly significant) |

Table 7: Complications

| Side effects | Number of patients affected | Treatment |
|--------------|-----------------------------|-----------|
| Bradycardia  | 2                           | Atropine 0.6 mg intravenous |
| Hypotension  | 0                           | 0         |
| Nausea/vomiting | 0                          | Ondansetron 4 mg intravenous |
| Pruritus     | 0                           | 0         |
| Others       | 0                           | 0         |

adrenoreceptor. Dalle et al. postulated that clonidine raises the action potential initiating threshold causing a block in conduction by causing hyperpolarisation generated by Na⁺-K⁺ during repetitive stimulation. Kosugi et al. studied complete action potential (CAPs) in the frog sciatic nerve and found that clonidine acts by inhibiting CAP.

Pöpping et al. found clonidine to be beneficial for prolonged duration of analgesia with all local anesthetics. El Saied AH et al. also showed an increase in analgesic duration from 587 to 828 min when clonidine was used for axillary plexus blockade.

Nishikawa et al. postulated three mechanisms for the analgesia produced by peripheral application of fentanyl. First, fentanyl acts directly on the peripheral nervous system. Primary afferent tissues (dorsal roots) have been found to contain opioid binding sites. Due to the presence of bidirectional axonal transport of opioid binding protein, fentanyl acts on the dorsal horn. This could account for the analgesic effect of fentanyl. Second, fentanyl may diffuse from the brachial plexus sheath to epidural and subarachnoid spaces and then bind with the opioid receptor of the dorsal horn. Third, fentanyl potentiates the action of local anesthetic by analgesia mediated by an opioid receptor that leads to fentanyl uptake into the systemic circulation.

During our study, we did not notice any significant change in systolic and diastolic blood pressure, and no patient in either group had hypotension (defined by decrease in blood pressure by 30%) and only two patients of clonidine group had bradycardia (defined by decrease in pulse rate by 20%) and required atropine i.v. This was statistically insignificant (P > 0.05) which is similar to a study conducted by Eisenach et al. Culebras et al. found that 150 µg of clonidine added to 40 cc 0.5% sensorcaine produced hemodynamic changes. The hemodynamic changes observed with the study of Culebras et al. were due to the huge dose of clonidine used in their study.

We observed a higher sedation score with the clonidine group (1.86 ± 0.34) compared to the fentanyl group (1.76 ± 0.43), but the difference between the two groups was clinically and statistically insignificant (P > 0.05). The result of our study is matched with the study done by Shah Alam et al. in 2008 who also showed that the prevalence of sedation was higher in the clonidine-bupivacaine group (40%) than fentanyl-bupivacaine group (33%) and they did not find any significant difference. No patient of any group had sedation score >2. This was in accordance with the publication of Neal et al. on upper extremity regional anesthesia that postulated that side effects (hypotension, bradycardia, sedation) do not occur up to a dose of 1.5 µg/kg or a maximum dose of 150 µg or less for clonidine, and in our study, we used a dose of 1 µg/kg clonidine as an adjuvant.

As evident from Table 7, we also observed nausea and vomiting in two patients with fentanyl who were treated with ondansetron 4 mg i.v. There were no other hemodynamic changes or complications. No patient of clonidine group had similar complaints. Hasan et al. also found no significant side effects on hemodynamic and respiratory parameters on adding opioids to local anesthetics and got minimal incidence of nausea and vomiting. Since we used very less dose of opioid and alpha-2 agonist as adjuvant, adverse effects are minimal.

The novelty of our study established is that fentanyl has a faster onset of sensory and motor blockade, while clonidine has a longer duration of sensory and motor blockade as well as prolonged analgesia. Both the drugs have a good safety profile and can be conveniently used...
to prolong duration of analgesia in the supraclavicular block.

Little sample size is the limitation of our study. Studies with bigger sample sizes are required for confirmation of our results; also, modern techniques like ultrasound were not available which would have reduced the dose of anesthetic agents.

CONCLUSION

We conclude that both clonidine and fentanyl in 1µg/kg as adjuvants to a mixture of local anaesthetics are without any side effects. Fentanyl has a faster onset of sensory and motor blockade, while clonidine ensures a longer duration of sensory and motor blockade as well as prolonged analgesia.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Research quality and ethics statement
This study was approved by the local Institutional Review Board / Ethics Committee. The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines, during the conduct of this research project.

REFERENCES

1. Gurajala I, Thripparampall AK, Durga P, Gopinath R. Effect of perineural dexmedetomidine on the quality of supraclavicular brachial plexus block with 0.5% ropivacaine and its interaction with general anaesthesia. Indian J Anaesth 2015;59:89-95.
2. Rashmi HD, Komala HK. Effect of dexmedetomidine as an adjuvant to 0.75% ropivacaine in interscalene brachial plexus block using nerve stimulator: A prospective, randomized double-blind study. Anesth Essays Res 2017;11:134-9.
3. Hajhasareef HM, Murugan T. Comparative study of ropivacaine 0.5% and ropivacaine 0.5% with dexmedetomidine 50 µg in ultrasound guided supraclavicular brachial plexus block for upper limb orthopaedic surgery. Int J Sci Stud 2017;4:169-75.
4. Shashikala TK, Madhyastha K. A prospective randomized double blinded study to evaluate the efficacy of dexmedetomidine 50 µg intravenously and perineurally as an adjunct to 0.5% ropivacaine for supraclavicular brachial plexus block. Anaesth Pain Intensive Care 2017;21:413-9.
5. Wu HH, Wang HT, Jin JJ, Cui GB, Zhou KC, Chen Y, et al. Does dexmedetomidine as a neuraxial adjuvant facilitate better anesthesia and analgesia? A systematic review and meta-analysis. PLoS One 2014;9:e93114.
6. Zainab F, Faruq MO, Talukder M, Yeasmeen S, Alam AK, Haque AK. Anaesthetic and analgesic effects of adding fentanyl to bupivacaine-lignocaine mixtures in supraclavicular brachial plexus block – A comparative study with or without fentanyl. Bangladesh Med J 2015;44:26-31.
7. Hasan S, Chowdhury AA, Khatoon SN, Rashid MH, Hoque MR, Billah KM. Efficacy and safety of fentanyl as an adjuvant with bupivacaine and lignocaine in supraclavicular brachial plexus block. Chattagram Maa O Shishu Hosp Med College J 2018;17:31-5.
8. Patocsil JA, McAuliffe MS, Feyh LS, Sigmun LL. Local anesthetic adjuvants providing the longest duration of analgesia for single-injection peripheral nerve blocks in orthopedic surgery: A literature review. AANA J 2016;84:95-103.
9. Verweylen K, De Puydt J, Engelen S, Rooftsooft E, Soetens F, Neyrinck A, et al. A double-blind randomized controlled trial comparing dexamethasone and clonidine as adjuvants to a ropivacaine sciatic popliteal block for foot surgery. Local Reg Anesth 2016;9:17-24.
10. Shah DM, Arora M, Trikha A, Prasad G, Sunder R, Kotwal P, et al. Comparison of dexamethasone and clonidine as an adjuvant to 1.5% lignocaine with adrenaline in infraclavicular brachial plexus block for upper limb surgeries. J Anaesthesiol Clin Pharmacol 2015;31:354-9.
11. Alarasan AK, Agrawal J, Choudhary B, Melhotra A, Ulke S, Mukherji A. Effect of dexamethasone in low volume supraclavicular brachial plexus block: A double-blinded randomized clinical study. J Anaesthesiol Clin Pharmacol 2016;32:234-9.
12. Huynh TM, Marret E, Bonnet F. Combination of dexamethasone and local anesthetic solution in peripheral nerve blocks: A meta-analysis of randomised controlled trials. Eur J Anaesthesiol 2015;32:751-8.
13. Ali QE, Manjunatha L, Amir SH, Jamil S, Quadir A. Efficacy of clonidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block: A prospective study. Indian J Anaesth 2014;58:709-13.
14. Chavan SG, Koshire AR, Panbude P. Effect of addition of fentanyl to local anesthetic in brachial plexus block on duration of analgesia. Anesth Essays Res 2011;5:39-42.
15. Chinnappa J, Shivanna S, Pujari VS, Anandaswamy TC. Efficacy of dexamethasemide with ropivacaine in supraclavicular brachial plexus block for upper limb surgeries. J Anaesthesiol Clin Pharmacol 2017;33:81-5.
16. Hamed MA, Ghaber S, Reda A. Dexmedetomidine and fentanyl as an adjunct to bupivacaine 0.5% in supraclavicular nerve block: A randomized controlled study. Anesth Essays Res 2018;12:475-9.
17. Pöpping DM, Elia N, Marret E, Wenk M, Tramer MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: A meta-analysis of randomized trials. Anesthesiology 2009;111:406-15.
18. Paluvadi VR, Manne VS. Effect of addition of fentanyl to xylocaine hydrochloride in brachial plexus block by supraclavicular approach. Anesth Essays Res 2017;11:121-4.
19. Singh G, Puri A. In ear surgeries intravenous dexamethasone preoperatively decreases post operative sore throat after endotracheal intubation in adult patients: a prospective randomized control study. Indian J Otolaryngol Head Neck Surg. 2020. https://doi.org/10.1007/s12070-019-01776-x.
20. Williams BA, Ibinson JW, Mangione MP, Scanlan RL, Cohen PZ. Clinical benchmarks regarding multimodal peripheral nerve blocks for postoperative analgesia: Observations regarding combined perineural midazolam-clonidine-buprenorphine-dexamethasone. Pain Med 2015;16:1-6.
21. Ilfeld BM. Continuous peripheral nerve blocks: A review of the published evidence. Anesth Analg 2011;113:904-25.
22. Patil KN, Singh ND. Clonidine as an adjuvant to ropivacaine-induced supraclavicular brachial plexus block for upper limb surgeries. J Anaesthesiol Clin Pharmacol 2015;31:365-9.
23. Rustagi P, Patekae GA, Malpani V, Tendolkar BA. Clonidine as an adjuvant to locoanalgestic in supraclavicular brachial plexus block: A randomized, double blinded placebo controlled study. Int J Basic Clin Pharmacol 2016;5:1892-7.
24. Bhatarai BK, Baral PR. Brachial plexus block as a sole anaesthetic technique in upper extremity fracture/dislocation in children: Subclavian perivascular vs parascalene approach. Kathmandu Univ Med J (KUMJ) 2006;4:426-30.
25. Ahmed NU. Addition of clonidine or fentanyl with bupivacaine for supraclavicular brachial plexus block-a randomized comparative study. JBSA 2011;24:23-7.
26. Jafa S, Kaashaal D, Singh V, SP Singh. Comparison of fentanyl – Bupivacaine and alkanized bupivacaine in supraclavicular brachial plexus block: A double-blinded randomized controlled study. Journal of anaesthesiology clinical pharmacology 2009:25-28.
Puri, et al.: A comparative study between fentanyl and clonidine as adjuvants to a mixture of local anaesthetics in potentiating postoperative analgesia in supraclavicular brachial plexus block

27. Moharari R, Sadeghi J, Khajavi M, Davari M, Mojtahedzadeh M. Fentanyl supplement expedites the onset time of sensory and motor blocking in interscalene lidocaine anesthesia. Daru 2010;18:298-302.
28. Dejong RH, Wagman IH. Physiological mechanisms of peripheral nerve block by local anesthetics. Anesthesiology 1963;24:684-727.
29. Dalle C, Schneider M, Clergue F, Bretton C, Jirounek P. Inhibition of the I (h) current in isolated peripheral nerve: A novel mode of peripheral antinociception? Muscle Nerve 2001;24:254-61.
30. Kosugi T, Mizuta K, Fujita T, Nakashima M, Kumamoto E. High concentrations of dexmedetomidine inhibit compound action potentials in frog sciatic nerves without alpha (2) adrenoceptor activation. Br J Pharmacol 2010;160:1662-76.
31. Nishikawa K, Kanaya N, Nakayama M, Igarashi M, Tsunoda K, Namiki A. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. Anesth Analg 2000;91:384-7.
32. Fields HL, Emson PC, Leigh BK, Gilbert RF, Iversen LL. Multiple opiate receptor sites on primary afferent fibres. Nature 1980;284:351-3.
33. Laduron PM. Axonal transport of opiate receptors in capsaicin-sensitive neurones. Brain Res 1984;294:157-60.
34. Eisenach JC, De Kock M, Klmscha W. Alpha (2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology 1996;85:655-74.
35. Culebras X, Van Gessel E, Hoffmeyer P, Gamulin Z. Clonidine combined with a long acting local anesthetic does not prolong postoperative analgesia after brachial plexus block but does induce hemodynamic changes. Anesth Analg 2001;92:199-204.
36. Neal JM, Gerancher JC, Hebl JR, Ilfeld BM, McCartney CJ, Franco CD, et al. Upper extremity regional anesthesia: Essentials of our current understanding. 2008. Reg Anesth Pain Med 2009;34:134-70.