ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Comparative evaluation of efficacy and duration of analgesia of clonidine and dexmedetomidine added to ropivacaine in supraclavicular brachial plexus block in upper extremity surgery

Anamitra Mandal[1], Sourav Naiya[2], Swarup Dutta[3], Sarbari Swaika[4], Swapnadeep Sengupta[5]

[1]Assistant Professor, Department of Anaesthesiology, Deben Mahata Government Medical College and Hospital, Pururlia, [2]Associate Professor, Department of Community Medicine, Murshidabad Medical College and Hospital, Baharampur, [3]Associate Professor, Department of Anaesthesiology, Bankura Sammilani Medical College and Hospital, Bankura, [5]Assistant Professor, Department of Anaesthesiology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, [4]Professor, Department of Anaesthesiology, Dr. D. Y. Patil Medical College, Pune, Maharashtra, India

Submission: 19-02-2025 Revision: 03-04-2025 Publication: 01-05-2025

ABSTRACT

Background: Supraclavicular brachial plexus block is a popular and widely employed regional nerve block technique for perioperative anesthesia and analgesia for surgery of the upper extremity. Local anesthetics alone for supraclavicular brachial plexus block provide good operative conditions but have a shorter duration of post-operative analgesia. Hence, various drugs as adjuvants were used with local anesthetics in the brachial plexus block to prolong the duration of analgesia and also hasten the onset of sensory and motor block. **Aims and Objectives:** To compare the onset of sensory block, the onset of motor block, and the duration of analgesia of clonidine and dexmedetomidine added to ropivacaine in supraclavicular brachial plexus block. **Materials and Methods:** The comparative study was carried out in a tertiary care hospital during 2012–2013 to find out the onset of sensory block, onset of motor block, duration of analgesia, and any adverse effects between two groups given a combination ropivacaine with dexmedetomidine and a combination of ropivacaine with clonidine. A total of 80 patients, 40 in each group were allotted randomly after taking informed consent and satisfying the inclusion and exclusion criteria. The efficacy and duration of analgesia between the two groups were assessed in supraclavicular brachial plexus block in upper extremity surgery. **Result:** The time of onset of sensory block (7.95 ± 2.029) and the onset of motor block (10.05 ± 2.025) was significantly less, and the time to rescue analgesic was significantly longer (563.25 ± 17.19) in ropivacaine–dexmedetomidine group in compare to ropivacaine–clonidine group. Bradycardia was found to be significantly more in the ropivacaine–dexmedetomidine group. **Conclusion:** Further studies are needed to determine the safe, optimal dose and effect of neurotoxicity of dexmedetomidine added to local anesthetics for supraclavicular brachial plexus block.

Key words: Analgesia; Brachial plexus block; Clonidine; Dexmedetomidine; Ropivacaine

Access this article online

Website: https://ajmsjournal.info/index.php/AJMS/index

DOI: 10.71152/ajms.v16i5.4469

E-ISSN: 2091-0576

P-ISSN: 2467-9100

Copyright (c) 2025 Asian Journal of Medical Sciences

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Address for Correspondence:
Dr. Anamitra Mandal, Assistant Professor, Department of Anaesthesiology, Deben Mahata Government Medical College and Hospital, Pururlia, West Bengal, India. **Mobile:** +91-9046141980. **E-mail:** anamitra84@gmail.com

INTRODUCTION

Upper limb surgeries are mostly performed under peripheral nerve blocks such as brachial plexus blocks. Peripheral nerve blocks not only provide intraoperative anesthesia but also extend analgesia in the post-operative period without any systemic side effects.[1] Among various approaches to brachial plexus block, the supraclavicular approach is considered the easiest and most effective. This approach provides the most complete and reliable anesthesia for upper extremity surgery as it is performed at the trunk level, where the brachial plexus is presented compactly. It provides excellent anesthesia for elbow, forearm, and hand surgery. The first supraclavicular brachial plexus block was performed by Kulenkampff in 1912.[2] The classical approach using the paraesthesia technique, being a blind technique, may be associated with a higher failure rate and injury to the nerves and vascular structures.[3] To avoid some of these problems, the use of a peripheral nerve stimulator was started which allowed for better localization of the nerves/plexus.[4] There has always been a search for adjuvants to the regional nerve block with drugs that prolong the duration of analgesia but with lesser adverse effects. The search for the ideal additive continues and led us to try the novel alpha-2 adrenergic agent, dexmedetomidine. Alpha-2 adrenergic receptor agonists have been the focus of interest for their sedative, analgesic, perioperative sympatholytic, and cardiovascular stabilizing effects with reduced anesthetic requirements. Furthermore, various methods of administration, such as epidural, intrathecal, and peripheral injections, have been tried either alone or in combination with another drug to prolong and intensify the anesthesia.[5]

Dexmedetomidine, a potent alpha-2 adrenoceptor agonist, is approximately 8 times more selective toward the α^2 adrenoceptor than clonidine.[6] In humans, dexmedetomidine has also been shown to prolong the duration of block and post-operative analgesia when added to local anesthetic in various regional blocks.[7] The current study was designed to test the hypothesis that dexmedetomidine, when added as an adjuvant to local anesthetic in supraclavicular brachial plexus block, enhanced the duration of sensory and motor block and duration of analgesia as compared with clonidine.

Aims and objectives

The objective of the study is to compare the onset of sensory block, onset of motor block and duration of analgesia of clonidine and dexmedetomidine added to ropivacaine in supraclavicular brachial plexus block.

MATERIALS AND METHODS

The comparative study was carried out in a medical college and hospital in West Bengal, India, during 2012–2013 after taking clearance from the Institutional Ethical Committee as per national laws and regulations and was designed to find out the onset of sensory block, onset of motor block, duration of analgesia and any adverse effects between two groups given a combination of ropivacaine with dexmedetomidine and a combination of ropivacaine with clonidine.

The sample size was calculated using the formula of $N=2\times \sigma^2 \times((Z_{1-\alpha}+Z_{1-\beta})/(\delta-\delta_0))^2$ considering the desired power of study 80%, α error 5%, and estimated effect size from a pilot study. Considering 10% to account for contingency, the sample size was 40 in each group. Eighty adult patients of 20–50 years of age who gave informed consent and of ASA physical status I and II, scheduled for upper limb orthopedic surgery were included in the study, excluding pregnant or lactating mothers and those who had known allergies to any of the drugs, infection at the site of the block, comorbid conditions, psychiatric disorder, coagulopathy or any bleeding disorder. The onset of sensory block was assessed, using a 3-point scale for pain (Gormley and Hill)[7] by pin-prick with a 23G needle, the onset of motor block was assessed by modified Lovett rating scale[8] and duration of analgesia was the endpoint when the patient required rescue analgesic. Patients were explained about the study, obtained informed consent, counseled, and demonstrated about the Visual Analog Scale and how to express the pain intensity during pre-anesthetic evaluation.

The 80 patients were randomly allocated into two groups, named "Group C" and "Group D." Group C (n=40) received ropivacaine (0.5%) 30 mL with clonidine (1 μg/kg body weight), and Group D (n=40) received ropivacaine (0.5%) 30 ml with dexmedetomidine (1 μg/kg body weight). The calculated dose of dexmedetomidine or clonidine, according to patient's body weight, was diluted with normal saline to make 1 mL of solution. Patients were monitored using standard monitoring guidelines. After aseptic preparation of the area, a supraclavicular brachial plexus block was performed using a nerve stimulator (Plexygon, 7501.31; Vygon, Italia S.r.l., Italy). Correct needle placement within the fascia was confirmed by the distal responses of the hand or wrist flexion or extension[9] and elbow flexion. Sensory and motor block of the nerves were determined at 0, 2, 4, 6, 8, 12, 15, 20, and 25 min after completion of injection. Sensory block was determined by response to pin-prick using a 3-point scale for pain (Gormley and Hill). Assessment of sensory block was done every 2 min, after completion of drug injection in the dermatomal areas, corresponding to the median nerve (thenar eminence), radial nerve (first web space), and ulnar nerve (hypothenar eminence) till complete sensory blockade. Assessment of motor block (by modified Lovett rating scale) was carried out every 2 min till complete

motor blockade after the drug injection. Motor block was evaluated by thumb abduction (radial nerve), thumb adduction (ulnar nerve), thumb opposition (median nerve), and flexion at the elbow (musculocutaneous nerve). A peak motor block was considered when there was a Grade 0 motor blockade. The onset time of sensory block was defined as the time interval between the end of local anesthetic injection and loss of sensation to pin-prick in all of the nerve distributions. The onset time of the motor block was defined as the time interval of completion of injection of the study drug to the first loss of motor power. Each patient was observed for complications such as bradycardia, hypotension, dizziness, dryness of mouth, and respiratory depression. The post-operative intensity of analgesia was evaluated using the Visual Analog Scale (ranging from 0 to 10), and rescue analgesic was given when the VAS score was >4 and the time was noted. The duration of analgesia was determined by the endpoint when the patient required the first rescue analgesic (injection of diclofenac 75 mg IM).

Ethics

Institutional Ethical Committee clearance (IEC no. 157/(01/31) dated January 13, 2012, BSMC, Bankura) as per national laws and regulations and the Helsinki Declaration was obtained before the study. Study participants were explained the purpose of the study and the risk-benefit of the procedure, and informed consent was obtained.

Statistics

Data were collected, compiled, and presented using tables and diagrams using Microsoft office© 2007, and appropriate statistical tests were done using Epi Info© version 6 software (Centers for Disease Control and Prevention). Descriptive parts of the results were represented with a mean (S.D), or number (percentage), and statistical analysis was done using independent samples t-test and Chi-square test where applicable.

RESULTS

A total of 80 patients were randomly allocated into two groups, whereas Group D received ropivacaine with dexmedetomidine for supraclavicular brachial plexus block, and Group C received ropivacaine with clonidine. The demographic profile of both groups was comparable with regard to age, weight, height, etc. The sex distribution was similar in both groups and the mean duration of surgery was comparable in both groups and was statistically non-significant (P>0.05) (Table 1).

Table 1: Comparison of demographic characteristics between two groups (n=80)

Variable	Group D* (n=40)	Group C* (n=40)	Statistics
	Mean±SD/ No (%)	Mean±SD/ No (%)	(P-value)*
Age	35.28±10.45	34.50±9.55	0.73
Height in cm	152.57±3.94	153.92±3.91	0.13
Weight in kg	54.37±5.29	54.80±4.42	0.69
Sex			
Male	24 (60)	26 (65)	χ^2=0.213, df=1, P=0.644
Female	16 (40)	14 (35)	

*Group D: Ropivacaine with dexmedetomidine, Group C: Ropivacaine with clonidine. Statistical tests used independent samples t-test, Chi-square test

Comparison of mean scores for onset of sensory block by a 3-point scale for pain (Gormley Hill) at different time points showing there was a significant difference between the groups at 2, 4, 6, 8, 10, 12, and 15 min (Figure 1) and comparison of scores for onset of motor block by Lovett rating scale at different times showing significant difference at 4, 6, 8, 10, 12, 15, and 20 min (independent t-test) (Figure 2).

The onset of both sensory block and motor block was faster and the duration of analgesia was longer in a ropivacaine-dexmedetomidine group compared to the ropivacaine-clonidine group. There was a significant difference with respect to the onset of sensory block, onset of motor block, and duration of analgesia between the two groups (Table 2). In our study, we found that the onset of sensory block was faster in Group D (7.95±2.02) compared to Group C (14.48±1.89), and this was statistically significant. The onset of the motor block was also faster in Group D (10.05±2.02) compared to Group C (19.97±2.72), and it was significant. The Visual Analog Score was also lower in Group D up to 15 min, and it was significant (at 10 min in Group D, the score was <1, whereas in Group C, it was >4). From 15 min up to 120 min in both groups, the Visual Analog Score was 0. Then again, it was rising in Group C (in Group D, the score was 1.12±0.82; in Group C, 2.07±0.97 at 6 h, and this was significant. The time to rescue analgesic was longer in Group D than in Group C. For Group D, it was 563.25±17.19 min, and for Group C, 478.375±14.69 min. This difference was statistically significant (Table 2).

In our study, bradycardia was found more in Group D which was statistically significant. Hypotension was found more in Group D but was not statistically significant. Few patients developed dizziness, but it was not statistically significant (Table 3). No patients developed dryness of mouth and respiratory depression.

DISCUSSION

In the context of perineural adjuvants, the efficacy of dexmedetomidine appears to be comparable with

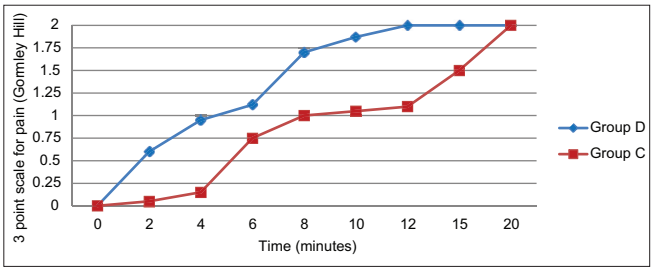

Figure 1: Comparison of mean scores for onset of sensory block (Gormley Hill) between two groups (n=80). *Group D: Ropivacaine with dexmedetomidine, Group C: Ropivacaine with clonidine

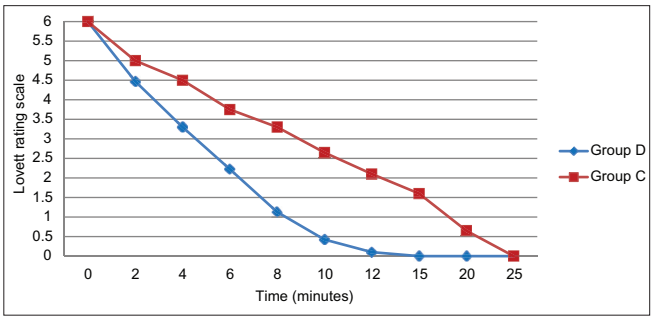

Figure 2: Comparison of mean scores for onset of motor block (Lovett rating scale) between two groups (n=80). *Group D: Ropivacaine with dexmedetomidine, Group C: Ropivacaine with clonidine

Table 2: Comparison of time of onset of sensory block, motor block, and duration of analgesia between two groups (n=80)

Variable	Group D*	Group C*	Statistics (P-value)*
	Mean±SD	Mean±SD	
Onset of sensory block (min)	7.95±2.029	14.48±1.89	<0.05
Onset of motor block (min)	10.05±2.02	19.97±2.72	<0.05
Time to rescue analgesia (min)	563.25±17.19	478.37±14.69	<0.05

*Group D: Ropivacaine with dexmedetomidine, Group C: Ropivacaine with clonidine. Statistical tests used independent samples t-test

Table 3: Comparison of incidence of side effects between two groups (n=80)

Side effects	Group D*	Group C*	Statistics (P-value)*
	No (%)	No (%)	
Bradycardia			
Yes	9 (22.5)	2 (5)	0.023
No	31 (77.5)	38 (95)	
Hypotension			
Yes	5 (12.5)	2 (5)	0.235
No	35 (87.5)	38 (95)	
Dizziness			
Yes	2 (5)	1 (2.5)	0.556
No	38 (95)	39 (97.5)	

*Group D: Ropivacaine with dexmedetomidine, Group C: Ropivacaine with clonidine. The statistical test used the Chi-square test. No case found with dryness of mouth and respiratory depression as a side effect

buprenorphine and dexamethasone when administered peripherally and exceeds that of peripheral applications of clonidine, magnesium, and midazolam.[10,11] Swami et al., in their study, found that the onset of sensory block was a little faster in the dexmedetomidine group as compared with the clonidine group, but it was statistically insignificant, while the onset of motor block was a little longer in dexmedetomidine group but not significant statistically.[12] Mandal et al. found that the onset of both sensory and motor block in the dexmedetomidine group was lower when in the clonidine group.[13]

In this study, the onset of sensory block and motor block was significantly faster in group D. Chakraborty et al. found that when clonidine added to bupivacaine was used for supraclavicular brachial plexus block, the onset of sensory and motor block was faster than the control group and, in clonidine group, sensory block was more rapid than motor block.[14] A study by Esmaoglu et al.,[7] and Kaygusuz et al.,[15] showed that when dexmedetomidine is used as an addition to local anesthetic, it can provide faster onset and longer duration for brachial plexus block, but resulted in some side effects, such as hypotension and bradycardia. Although, Gandhi et al in their study observed that the onset of a motor block was faster than a sensory block when they used dexmedetomidine as an adjuvant to bupivacaine for brachial plexus block.[16] This may be explained by the "core and mantle" concept of Winnie et al.,[17,] which states that outer motor fibers of the brachial plexus form the mantle and are blocked earlier than the sensory fibers at the core. That is why the onset of motor blockade was significantly faster than that of sensory block.[17] Saied et al., in their study, did not notice any difference in onset time in the clonidine-ropivacaine group compared to the control group.[18]

Time to rescue analgesic was found to be significantly longer in Group D than in Group C in our study. This finding corroborates with the study by Swami et al. (for Group D, 456.21±97.99 min; for Group C, 289.67±62.5 min, which was statistically significant).[12] Abdallah and Brull reviewed that there was an increase in time to the first analgesic request by 345 min in the dexmedetomidine group as compared to local anesthetics alone.[19] Kumari et al. also found in their study that the ropivacaine–dexmedetomidine group provided earlier sensory block and prolonged post-operative analgesia as compared to the ropivacaine-clonidine group.[20] Mandal et al. concluded that the duration of sensory block and duration of analgesia in the dexmedetomidine group was considerably prolonged when compared with the clonidine group.[13] Natarajan et al. found that dexmedetomidine prolonged the duration of the sensory and motor block as well as the duration of post-operative analgesia as compared to clonidine when used as

an adjuvant to ropivacaine in supraclavicular brachial plexus block and no significant post-operative complications or local side effects related to the block were noted.[21]

Limitations of the study

The major limitation of our study was that we did not use ultrasound-guided blocks because of unavailability at the time of our study; this could have helped us to lower dosages and volumes of local anesthetic. Despite an intensive search of the published literature, we were unable to identify an ideal scale for assessment of the quality of the block achieved. While the higher cost of dexmedetomidine can be suggested as a reason for the preference for clonidine. Further studies to determine the cost-effectiveness of the drugs are necessary. From this study, we would like to suggest that dexmedetomidine can be safely used with local anesthetic in peripheral nerve blocks; however, further trials to determine the exact dose-response and effects on complex nerve structures, such as in brachial plexus blocks are necessary.

CONCLUSION

Dexmedetomidine, when added to ropivacaine in the supraclavicular brachial plexus block, enhances the onset of sensory and motor block. The time for rescue analgesia was prolonged in patients receiving dexmedetomidine compared with clonidine. Perineural dexmedetomidine produces some side effects (hypotension and bradycardia) more than clonidine, but these can be reversed easily by medication. Side effects may be associated with dosage or individual sensitivity. Further studies are needed to determine the safe, optimal dose of dexmedetomidine added to local anesthetics for supraclavicular brachial plexus block, and further studies to determine the effect of neurotoxicity on the human nerve are required.

ACKNOWLEDGMENT

None.

REFERENCES

1. Murphy DB, McCartney CJ and Chan VW. Novel analgesic adjuncts for brachial plexus block: A systematic review. Anesth Analg. 2000;90(5):1122-1128.
   https://doi.org/10.1097/00000539-200005000-00023
2. Lee JA, Atkinson RS and Rushman GB. A Synopsis of Anaesthesia. 10th ed. London: Wright; 1987. p. 618.
3. Carty S and Nicholls B. Ultrasound-guided regional anaesthesia. Contin Educ Anaesth Crit Care Pain. 2007;7(1):20-24.
   https://doi.org/10.1093/bjaceaccp/mkl059
4. Haleem S, Siddiqui AK, Mowafi HA, Ismail SA and Ali QA. Brief reports: Nerve stimulator evoked motor response predicting a successful supraclavicular brachial plexus block. Anesth Analg. 2010;110(6):1745-1746.
   https://doi.org/10.1213/ANE.0b013e3181da82ff
5. Popping DM, Elia N, Marret E, Wenk M and Tramèr MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: A meta-analysis of randomized trials. Anesthesiology. 2009;111(2):406-415.
   https://doi.org/10.1097/ALN.0b013e3181aae897
6. Virtanen R, Savola JM, Saano V and Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. Eur J Pharmacol. 1988;150 (1-2):9-14.
   https://doi.org/10.1016/0014-2999(88)90744-3
7. Esmaoglu A, Yegenoglu F, Akin A and Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anaesth Analg. 2010;111(6):1548-1551.
   https://doi.org/10.1213/ANE.0b013e3181fa3095
8. Duma A, Urbanek B, Sitzwohl C, Kreiger A, Zimpfer M and Kapra S. Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: A randomized, controlled study. Br J Anaesth. 2004;94(1):112-116.
   https://doi.org/10.1093/bja/aei009
9. Tsui BC and Rosenquist RW. Peripheral nerve blockade. In: Barash PG, editor. Clinical Anaesthesia. 6th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2009. p. 973.
10. Cummings KC 3rd, Napierkowski DE, Parra-Sanchez I, Kurz A, Dalton JE, Brems JJ, et al. Effect of dexamethasone on the duration of interscalene nerve blocks with ropivacaine or bupivacaine. Br J Anaesth. 2011;107(3):446-453.
    https://doi.org/10.1093/bja/aer159
11. McCartney CJ, Duggan E and Apatu E. Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. Reg Anesth Pain Med. 2007;32(4):330-338.
    https://doi.org/10.1016/j.rapm.2007.02.010
12. Swami SS, Keniya VM, Ladi SD and Rao R. Comparison of dexmedetomidine and clonidine (α^2 agonist drugs) as an adjuvant to local anaesthesia in supraclavicular brachial plexus block: A randomised double-blind prospective study. Indian J Anaesth. 2012;56(3):243-249.
    https://doi.org/10.4103/0019-5049.98767
13. Mandal S, Maitra S, Mukherjee A and Mandal M. Clonidine and dexmedetomidine as adjuvant to ropivacaine for supraclavicular brachial plexus block during upper limb surgery: A comparative study. Asian J Med Sci. 2022;13(7):34-42.
    https://doi.org/10.3126/ajms.v13i7.44299
14. Chakraborty S, Chakrabarti J, Mandal MC, Hazra A and Das S. Effect of clonidine as adjuvant in bupivacaine-induced supraclavicular brachial plexus block: A randomized controlled trial. Indian J Anaesth. 2010;42(2):74-77.
    https://doi.org/10.4103/0253-7613.64498
15. Kaygusuz K, Kol IO, Duger C, Gursoy S, Ozturk H, Kayacan U, et al. Effects of adding dexmedetomidine to levobupivacaine in axillary brachial plexus block. Curr Ther Res. 2012;73(3):103-111.
    https://doi.org/10.1016/j.curtheres.2012.03.001
16. Gandhi R, Shah A and Patel I. Use of dexmedetomidine along with bupivacaine for brachial plexus block. Natl J Med Res. 2012;2(1):67-69.
17. Winnie AP, Radonjic R, Akkineni SR and Durrani Z. Factors influencing distribution of local anesthetic injected into the brachial plexus sheath. Anesth Analg. 1979;58(3):225-234.
18. El Saied AH, Steyn MP and Ansermino JM. Clonidine prolongs

the effect of ropivacaine for axillary brachial plexus blockade. Can J Anaesth. 2000;47(10):962-967.

https://doi.org/10.1007/BF03024866

19. Abdallah FW and Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: A systematic review and meta-analysis. Br J Anaesth. 2013;110(6):915-925.

https://doi.org/10.1093/bja/aet066:1-11

20. Kumari P, Singh RB, Saurabh K, Pal S, Ram GK and Anand RK. To compare the efficacy of postoperative analgesia between clonidine and dexmedetomidine as adjuvants with 0.5% ropivacaine by ultrasound-guided supraclavicular brachial plexus block for upper limb surgeries: A prospective, double-blind, randomized study. Anesth Essays Res. 2020;14(4):644-652.

https://doi.org/10.4103/aer.aer_57_21

21. Natarajan NA, Kuppusamy GO, Ramanathan AI and Dave SM. A comparative study of dexmedetomidine and clonidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block. Asian J Pharm Clin Res. 2022;15(2):119-122.

Authors' Contributions:
AM- Definition of intellectual content, literature survey, preparation of the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation, and submission of the article; **SN**- Design, data analysis, manuscript preparation, editing, manuscript revision, statistical analysis, and interpretation; **SS**- Design of study and review manuscript; **SD**- Review manuscript; **SS**- Editing and manuscript revision.

Compliance with ethical standards:
Study approved by Institute Ethical Committee

Work attributed to:
Bankura Sammilani Medical College and Hospital, Bankura, West Bengal, India.

Orcid ID:
Anamitra Mandal - https://orcid.org/0009-0001-7701-2056
Sourav Naiya - https://orcid.org/0009-0001-7559-024X
Swarup Dutta - https://orcid.org/0000-0002-1493-7270
Sarbari Swaika - https://orcid.org/0000-0002-0525-8460
Swapnadeep Sengupta - https://orcid.org/0000-0001-8594-4315

Source of Support: Nil, **Conflicts of Interest:** None declared.