

Comparative Study of Clonidine and Dexmedetomidine as an Adjuvant to Bupivacaine in Supraclavicular Brachial PlexusPooja J Patel¹, S. Sowmya², Ankur F Chaudhari^{3*}¹ Assistant Professor, Department of Anaesthesia, NAMO Medical Education and Research Institute, Silvassa, Dadra and Nagar Haveli and Daman and Diu, India² Resident Doctor, Department of Anaesthesia, NAMO Medical Education and Research Institute, Silvassa, Dadra and Nagar Haveli and Daman and Diu, India³ Assistant Professor, Department of Pharmacology, GMERS Medical College, Valsad, Gujarat, India

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Abstract:

Introduction: The administration of local anesthetics for regional anesthesia has evolved over the years, with the quest for optimal adjuvants to enhance the quality and duration of nerve blocks. Interest lies in using adjuvants like clonidine and dexmedetomidine to enhance supraclavicular brachial plexus blocks for upper limb surgeries. This study aims to conduct a comparative analysis of clonidine and dexmedetomidine as adjuvants to bupivacaine in supraclavicular brachial plexus blocks, shedding light on their efficacy, safety, and clinical outcomes.

Material and Methods: In this study, 80 patients, classified as ASA Grade I and II, undergoing upper limb orthopedic surgeries, received a supraclavicular brachial plexus block (SBPB). They were randomly divided into two groups: Group C (n = 40) received bupivacaine 0.25% with clonidine, and Group D (n = 40) received bupivacaine 0.25% with dexmedetomidine. The patients were assessed for sensory and motor blocks, vital signs, and pain levels at various time points. Adverse events were monitored, and the quality of anesthesia was evaluated. Statistical analysis was performed using Student's t-test and the Chi-square test.

Results: Group D (Dexmedetomidine) showed a faster onset of sensory block (1.76 minutes vs. 3.55 minutes) and motor block (3.45 minutes vs. 4.16 minutes) compared to Group C (Clonidine), although these differences were not statistically significant ($p > 0.05$). However, Group D had significantly longer durations for both sensory and motor blocks (467 min vs. 312 min and 490 min vs. 329 min, respectively) compared to Group C ($p < 0.05$). Additionally, Group D exhibited a substantially extended duration of analgesia (478 min vs. 321.16 min) compared to Group C ($p < 0.05$). Moreover, throughout the study, Dexmedetomidine consistently maintained a more pronounced and sustained reduction in pulse rate compared to Clonidine, which could be particularly relevant in scenarios requiring prolonged hemodynamic control.

Conclusion: Dexmedetomidine outperformed clonidine in enhancing the effectiveness and duration of supraclavicular brachial plexus blocks, making it a preferable choice for such procedures, particularly in scenarios requiring prolonged hemodynamic control.

Keywords: Dexmedetomidine, Clonidine, Brachial Plexus Block.

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Introduction

The use of regional anesthesia techniques has evolved significantly in recent years, providing effective pain relief and minimizing the need for systemic analgesics in various surgical procedures.[1] Supraclavicular brachial plexus block (SBPB) has gained prominence as a preferred choice for upper limb surgery due to its reliable anesthesia and analgesia for the entire upper extremity.[2] To enhance the quality and duration of the block, adjuvants such as clonidine and dexmedetomidine have been investigated.[3,4] These alpha-2 adrenergic agonists exhibit sedative, analgesic, and sympatholytic properties, making

them promising candidates for improving the efficacy of SBPB.[5]

Clonidine and dexmedetomidine, both classified as alpha-2 adrenergic agonists, stand out for their multifaceted pharmacological properties, which encompass sedation, analgesia, and sympathetic nervous system modulation.[6,7] These attributes render them highly promising contenders for augmenting the efficacy of SBPB. Nonetheless, the decision between these two adjuvants remains a topic of spirited debate within the medical community, necessitating an exhaustive and

methodical comparison of their respective impacts on SBPB.[8]

In consideration of these factors, the primary objective of our study is to undertake a rigorous comparative analysis of clonidine and dexmedetomidine as adjuncts to bupivacaine in the context of SBPB. Our hypothesis posits that these adjuvants will confer improvements in both the duration and efficacy of the block, albeit with potentially divergent impacts on hemodynamic stability and the incidence of adverse events. The overarching aim of this investigation is to elucidate the nuanced merits and demerits associated with each adjuvant, thereby advancing the scientific knowledge base in the realm of regional anesthesia and offering clinicians evidence-based insights to inform their decision-making processes and optimize patient care.

Material and Method

A total of eighty patients, categorized as American Society of Anesthesiologists Grade I and II, were included in the study, comprising both male and female individuals aged between 21 and 60 years. These patients were scheduled for moderate orthopedic surgeries involving the upper limb and were subjected to a supraclavicular brachial plexus block (SBPB). Exclusion criteria encompassed medical histories involving cardiac, respiratory, hepatic, or renal disorders, pregnancy, known sensitivities or allergies to study medications, as well as contraindications to brachial plexus block such as clotting disorders, local infections, or patient refusal. Comprehensive explanations of the anesthetic procedure and study protocols were provided to patients during their preoperative visits.

The eighty patients were randomly assigned to two groups, each consisting of forty participants. Group C (n = 40) received 39 ml of bupivacaine 0.25% with 1 ml (1 µg/kg) of clonidine, while Group D (n = 40) received 39 ml of bupivacaine 0.25% with 1 ml (1 µg/kg) of dexmedetomidine, and blinding was meticulously maintained throughout the administration process.

Prior to surgery, all patients observed a fasting period of 6–8 hours. Upon arrival in the anesthetic room, intravenous access was established via an 18G cannula in the nonoperated arm, and lactated Ringer's solution was initiated. Patients received premedication with 2 mg of intravenous midazolam. Baseline measurements of heart rate (HR), noninvasive blood pressure, and oxygen saturation (SpO₂) were documented before the commencement of the block.

Under stringent aseptic conditions, the supraclavicular brachial plexus block was performed with patients in the supine position. Neural localization was accomplished using a nerve

stimulator connected to a 22G, 55 mm long stimulating needle. The needle placement was considered appropriate when an output current of 0.5 mA induced a slight distal motor response. Sensory and motor blocks were assessed at 3-minute intervals during the initial 30 minutes following drug administration.

Perioperative monitoring involved the recording of vital parameters (PR, BP, and SpO₂) every 5 minutes during the first 30 minutes and subsequently every 10 minutes until the conclusion of surgery. Post-surgery, sensory and motor blockade, as well as vital parameters, were assessed at 10 minutes, 30 minutes, and 1, 2, 4, 6, and 12 hours postoperatively. Sensory block was evaluated using the pinprick test and categorized as follows: Grade 0 = no sensation, Grade 1 = dull sensation, Grade 2 = sharp pain. Motor block was assessed using a modified Bromage scale (3 = full extension of elbow against gravity, 2 = flexion of wrist against gravity, 1 = finger movement, and 0 = no movement).[8]

The onset of sensory block was defined as the time from the injection of local anesthetic until no response to the pinprick test was observed, while the onset time of motor block was defined as the time between injection and the onset of motor paralysis. The duration of sensory block referred to the interval from complete sensory block to the onset of the first postoperative pain, whereas the duration of motor block was defined as the time interval between complete motor paralysis and full motor function recovery. Postoperative pain levels were measured using a 10 cm visual analog scale (VAS) ranging from 0 (no pain) to 10 (severe pain). In cases where the VAS exceeded 4, 75 mg of diclofenac was administered intramuscularly as a rescue analgesic. The time to the first analgesic request was recorded, and the duration of analgesia was calculated as the time between the end of local anesthetic administration and the first analgesic request. Adverse events encompassed hypotension (defined as a 20% decrease from baseline blood pressure), bradycardia (HR <50 beats/min), hypoxemia (SpO₂ < 90%), or nausea and vomiting. At the conclusion of surgery, the quality of anesthesia was assessed using a numeric scale: 4 = excellent (no patient complaints), 3 = good (minor complaints with no supplemental analgesia required), 2 = moderate (complaints necessitating supplemental analgesics), and 1 = unsuccessful (patient received general anesthesia).[9]

Statistical analyses were performed using Student's t-test and the Chi-square test, with statistical significance defined as $p < 0.05$.

Results

Patients in both Group C (Clonidine) and Group D (Dexmedetomidine) exhibited comparable demographic characteristics. (Table 1) There were

no significant differences between the groups in terms of age, sex distribution, weight, height, ASA status, or the distribution of surgery types. (p>0.05)

Table 1: Patient demographic characteristics

Characteristic	Group C (Clonidine)	Group D (Dexmedetomidine)	p-value
Age (years)	37.46±9.36	36.76±11.46	0.73
Sex (M/F)	28/12	26/14	0.35
Weight (kg)	60.36±15.46	59.16±12.35	0.67
Type of Surgery			
Lower end of Humerus #	21	18	
Olecranon #	14	15	
Radius & Ulna #	5	7	
Height (cm)	157.43±6.58	158.33±5.67	0.56
ASA Status (I/II)	39/1	38/2	0.35

Table 2 presents vital data concerning sensory and motor block onset times, block durations, and analgesia durations in two study groups: Group C (Clonidine) and Group D (Dexmedetomidine). Notably, Group D exhibited a significantly quicker onset of sensory and motor blocks, with p-values of 0.075 and 0.345, respectively, compared to Group C.

Moreover, Group D displayed significantly longer durations for both sensory and motor blocks, supported by p-values of 0.001 each, when contrasted with Group C. Additionally, Group D demonstrated a substantially extended duration of analgesia, with a p-value of 0.001, compared to Group C.

Table 2: Sensory and motor block onset time, block and analgesia durations in both groups

Variables	Group C (Clonidine)	Group D (Dexmedetomidine)	p-value
Onset of sensory block (min)	3.55±1.21	1.76±2.12	0.075
Onset of motor block (min)	4.16±2.12	3.45±3.53	0.345
Duration of sensory block (min)	312±57.32	467±17.63	0.001
Duration of motor block (min)	329±34.65	490±41.88	0.001
Duration of analgesia (min)	321.16±36.12	478±36.12	0.001

In present study, Dexmedetomidine (Group D) consistently demonstrated a more pronounced and sustained reduction in pulse rate compared to Clonidine (Group C) throughout the study (Figure 1), suggesting that Dexmedetomidine may be a more

effective choice for maintaining lower heart rates over an extended period, which could be especially relevant in clinical scenarios requiring prolonged hemodynamic control.

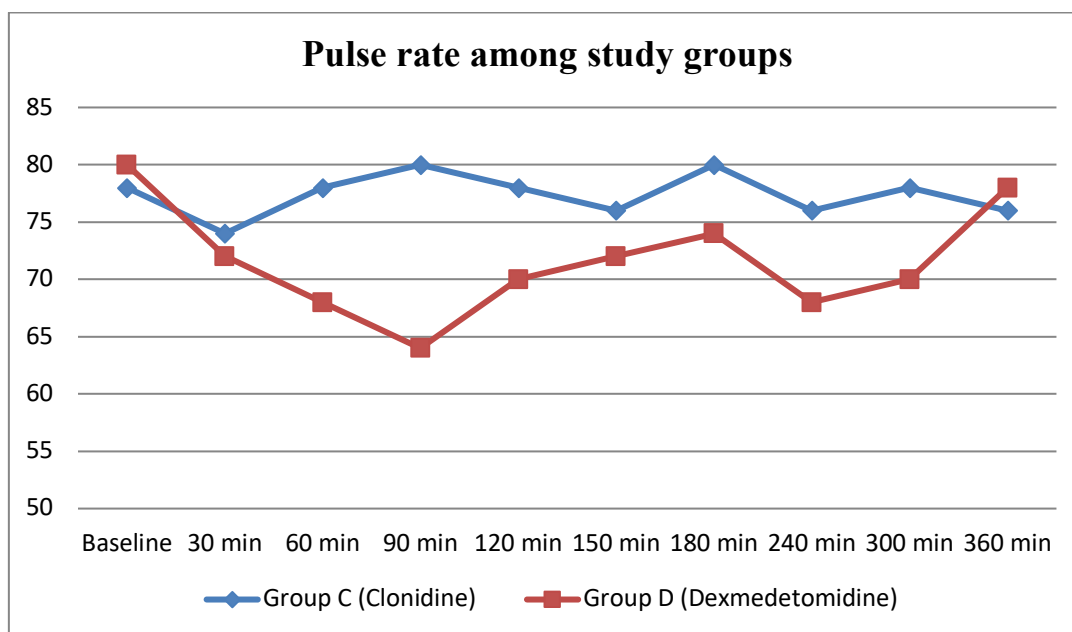


Figure 1: Pulse rate among study groups

In Figure 2, the data shows the blood pressure values for two groups, SBP Dex (Dexmedetomidine) and SBP Clonidine (Clonidine), as well as DBP Dex (Dexmedetomidine) and DBP Clonidine (Clonidine), at various time points. Dexmedetomidine (SBP Dex and DBP Dex) consistently maintained lower blood pressure values compared to Clonidine (SBP Clonidine and DBP Clonidine) over the entire study period, suggesting its potential effectiveness in achieving better blood pressure control in clinical settings requiring prolonged monitoring and management.

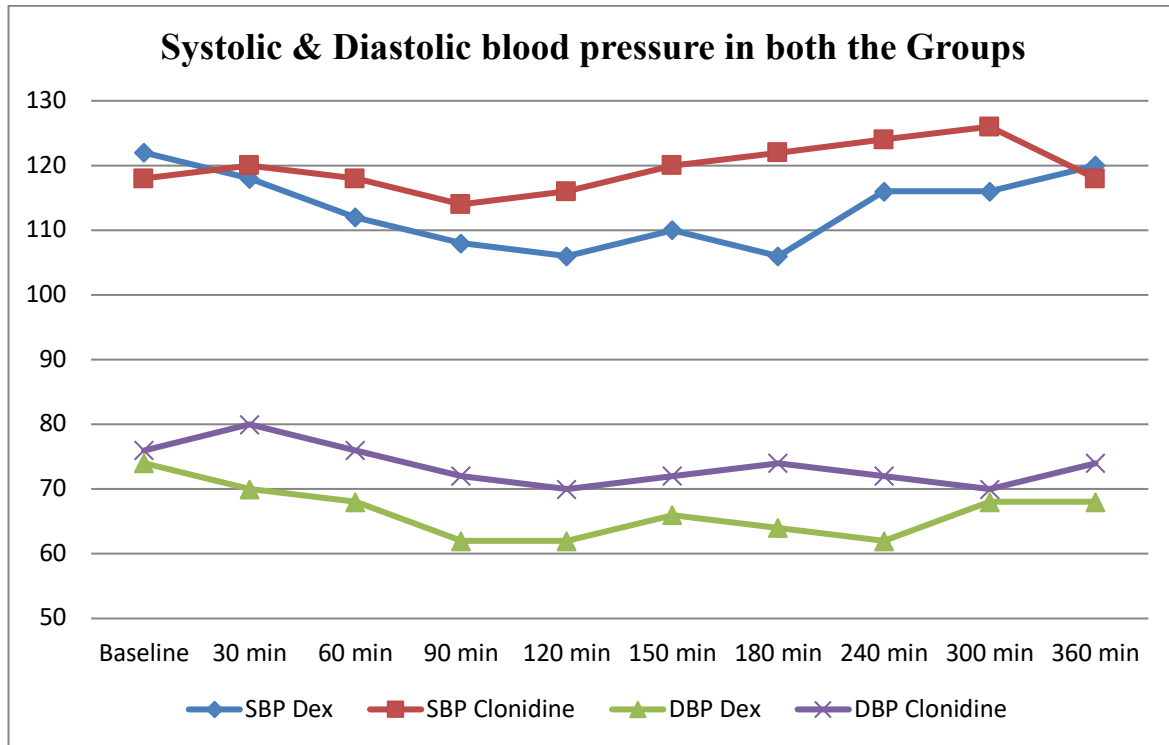


Figure 2: Systolic & Diastolic blood pressure in both the groups

In term of quality of anesthesia, group D demonstrated a significantly higher percentage of Grade 4 anesthesia (70%) compared to group C (47.5%), indicating a superior quality of anesthesia. ($P < 0.05$) Additionally, group C had a higher percentage of Grade 3 anesthesia (52.5%) compared to group D (30%). During both the intraoperative and postoperative periods, none of the patients required treatment for hypotension, bradycardia, or hypoxemia. Additionally, no patients in either group experienced side effects such as drowsiness, nausea, vomiting, or dry mouth within the initial 24 hours following surgery.

Discussion

In our study, which compared Clonidine and Dexmedetomidine as adjuvants in supraclavicular brachial plexus blocks, we found that Dexmedetomidine consistently maintained lower blood pressure values and exhibited a sustained reduction in pulse rate compared to Clonidine throughout the study. This suggests that Dexmedetomidine may be a more effective choice for achieving hemodynamic control and stable heart rates in clinical scenarios requiring prolonged monitoring and management.

In our study, we meticulously examined the onset of sensory and motor blocks in patients receiving anesthesia regimens of Group C (Clonidine) and Group D (Dexmedetomidine). Our findings indicated no statistically significant difference in the onset of sensory or motor blocks between these two groups, as demonstrated by p-values of 0.075 and 0.345, respectively.

Our results align with the findings of Tripathi et al.[10], who also reported no statistically significant disparities in sensory and motor block onset times in their study. However, the literature offers diverse perspectives on this matter. Swami et al.[11] suggested a faster onset of sensory block in Group D compared to Group C, with a reciprocal trend for motor block onset, though these differences were not statistically significant ($P > 0.001$). Meanwhile, Vania et al.[12] and Chaudhary et al.[13] presented somewhat conflicting results, reporting variations in onset times, yet without significant differences between the groups.

In our study, we evaluated the duration of sensory and motor blocks, as well as the duration of analgesia, in patients receiving anesthesia regimens of Group C (Clonidine) and Group D (Dexmedetomidine). Our findings showed

significant differences between the two groups, with Group D demonstrating notably prolonged sensory block duration (467.00 ± 17.63 min) compared to Group C (312.00 ± 57.32 min), as well as longer motor block duration (490.00 ± 41.88 min) compared to Group C (329.00 ± 34.65 min). Similarly, the duration of analgesia was significantly longer in Group D (478.00 ± 36.12 min) than in Group C (321.16 ± 36.12 min), all with p-values of 0.001.

These findings are consistent with the observations made by Tripathi et al.[10], who reported significantly prolonged sensory and motor block durations in Group D compared to Group C, along with a longer duration of analgesia in the Dexmedetomidine group. It's noteworthy that in all patients in our study and Tripathi et al.'s[10] study, the blocks were successful.

Another study by Swami et al.[11] also noted a statistically significant difference in sensory block duration, favoring Group D, which mirrors our findings. Additionally, Kirubahar et al.[14] observed similar trends, with Group D showing significantly longer durations of sensory and motor blocks as well as analgesia compared to Group C. Chaudhary et al.'s[13] study, too, confirmed the prolonged duration of sensory and motor blocks in the Dexmedetomidine group compared to Clonidine. Collectively, these results suggest that Dexmedetomidine consistently extends the duration of sensory and motor blocks and provides longer-lasting analgesia compared to Clonidine. These findings have important implications for clinicians seeking to optimize regional anesthesia techniques and may influence the choice of adjuvants in clinical practice.

The existing body of research provides compelling insights into the mechanisms and clinical effects of α -2 adrenoreceptor agonists, specifically Clonidine and Dexmedetomidine, as adjuvants to local anesthetics. These animal studies[15,16] and clinical trials[17] collectively emphasize their ability to enhance analgesic efficacy when added to local anesthetics, with effects mediated through α -2 adrenoreceptors. Notably, Dexmedetomidine exhibits greater selectivity for α -2 adrenoreceptors compared to Clonidine. Human studies[18,19] further underline the clinical significance of these findings. Dexmedetomidine, in particular, emerges as a superior neuraxial adjuvant, providing early sensory analgesia onset, prolonged postoperative analgesia, and improved anesthesia quality when compared to Clonidine. However, it's worth noting that in some specific contexts, such as pediatric caudal anesthesia, there may be no significant difference in duration of analgesia between the two agents.

While previous investigations have explored the effects of Clonidine and Dexmedetomidine in various regional and neuraxial anesthesia techniques[9,20], our study's focus on their comparative use as adjuvants to bupivacaine in supraclavicular brachial plexus block is a novel contribution to the literature. This approach was based on the premise that Dexmedetomidine, with its higher selectivity for α -2 adrenoreceptors, may offer advantages in this particular application.¹⁹ Nonetheless, there remains a need for further research to fully elucidate the multifactorial mechanisms by which α -2 adrenoreceptor agonists produce analgesia and sedation, especially in peripheral nerve blocks.

In our study, we observed distinct patterns in blood pressure and pulse rate dynamics between Dexmedetomidine (Group D) and Clonidine (Group C). Dexmedetomidine consistently maintained lower blood pressure values throughout the study, indicating its potential efficacy in achieving superior blood pressure control in settings demanding prolonged monitoring and management. Moreover, Dexmedetomidine exhibited a sustained reduction in pulse rate compared to Clonidine, suggesting its suitability for maintaining lower heart rates over an extended duration, which could be particularly beneficial in scenarios requiring prolonged hemodynamic stability.

These findings align with the observations made by Tripathi et al.[10], where significant reductions in pulse rate and blood pressure were noted in the Dexmedetomidine group compared to the Clonidine group up to 90 minutes, although no treatment was required to manage these changes. Similarly, Swami et al. reported a significantly lower pulse rate and blood pressure in the Dexmedetomidine group, particularly from 30 to 120 minutes, without the need for intervention. Ultimately, our study contributes to the growing body of evidence highlighting the potential advantages of Dexmedetomidine over Clonidine in achieving hemodynamic control and stable heart rates during anesthesia and postoperative care.

The peripheral actions of Clonidine[16,21,22] and Dexmedetomidine[16,23] in nerve blocks have been extensively studied. Clonidine's mechanisms involve enhancing activity-dependent hyperpolarization and inhibiting nerve conduction, while Dexmedetomidine enhances hyperpolarization-activated cation currents to prolong nerve block duration. Importantly, Dexmedetomidine has been shown to have a peripheral effect that is dose-dependent and not mediated centrally or systemically. These mechanisms align with findings in our study, where Dexmedetomidine demonstrated a statistically significant advantage in the duration of analgesia compared to Clonidine, alongside stable

hemodynamics and improved anesthesia quality (Peripheral action of Clonidine; Peripheral action of Dexmedetomidine).

Our study contributes to the understanding of Clonidine and Dexmedetomidine's peripheral actions, suggesting their potential as valuable adjuvants in peripheral nerve blocks. While Dexmedetomidine exhibited central sedative effects in some patients, it did not compromise their comfort during surgery. These findings underscore the potential clinical benefits of Dexmedetomidine in achieving prolonged analgesia with minimal side effects, adding to the growing body of knowledge in this field.

Conclusion

In conclusion, our study reveals valuable insights into the comparative efficacy of Clonidine and Dexmedetomidine as adjuvants in supraclavicular brachial plexus blocks. Dexmedetomidine demonstrated superior hemodynamic control, maintaining lower blood pressure values and a sustained reduction in pulse rate compared to Clonidine, which could be advantageous in scenarios requiring prolonged monitoring and stable heart rates. Although both agents exhibited similar onset times for sensory and motor blocks, Dexmedetomidine significantly prolonged the duration of sensory and motor blocks, as well as analgesia, with improved anesthesia quality.

Bibliography

- Kehlet H, Wilkinson RC, Fischer HBJ, Camu F, Prospect Working Group. PROSPECT: evidence-based, procedure-specific postoperative pain management. *Best practice & research Clinical anaesthesiology*. 2007;21(1):149–59.
- Chinnappa J, Shivanna S, Pujari VS, Anandaswamy TC. Efficacy of dexmedetomidine with ropivacaine in supraclavicular brachial plexus block for upper limb surgeries. *Journal of Anaesthesiology, Clinical Pharmacology*. 2017;33(1):81.
- Honnannavar KA, Mudakanagoudar MS. Comparison between conventional and ultrasound-guided supraclavicular brachial plexus block in upper limb surgeries. *Anesthesia, essays and researches*. 2017;11(2):467.
- Patil S, Koshire A. Comparison of success rate of classical supraclavicular brachial plexus block with and without nerve stimulator. *MVP Journal of Medical Sciences*. 2017;135–40.
- Murthy T, Singh R. Alpha 2 adrenoceptor agonist-dexmedetomidine role in anaesthesia and intensive care: A clinical review. *Journal of Anaesthesiology Clinical Pharmacology*. 2009;25(3):267–72.
- Mantz J, Jossierand J, Hamada S. Dexmedetomidine: new insights. *European Journal of Anaesthesiology| EJA*. 2011;28(1):3–6.
- Giovannitti Jr JA, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesthesia progress*. 2015;62(1):31–8.
- El Saied A, Steyn M and, Ansermino J. Clonidine prolongs the effect of ropivacaine for axillary brachial plexus blockade. *Canadian Journal of Anesthesia*. 2000;47:962–7.
- Memis D, Turan A, Karamanlioglu B, Tükenmez B, Pamukçu Z. The effect of tramadol or clonidine added to intraperitoneal bupivacaine on postoperative pain in total abdominal hysterectomy. *Journal of opioid management*. 2005;1(2):77–82.
- Tripathi A, Sharma K, Somvanshi M, Samal RL. A comparative study of clonidine and dexmedetomidine as an adjunct to bupivacaine in supraclavicular brachial plexus block. *Journal of anaesthesiology, clinical pharmacology*. 2016;32(3):344.
- Swami SS, Keniya VM, Ladi SD, 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 journal of anaesthesia*. 2012;56(3):243.
- Kanvee V, Patel K, Doshi M, Mayur V, Kapil G. Comparative study of clonidine and dexmedetomidine as an adjuvant with ropivacaine in supraclavicular brachial plexus block for upper limb surgery. *J Res Med Dent Sci*. 2015;3:127.
- Chaudhary UK, Danesh A, Mahajan M, Kumar S, Verma V, Awasthi B. Comparison of effects of dexmedetomidine and clonidine as adjuvant to bupivacaine 0.25% in ultrasound guided supraclavicular brachial plexus block. *Int J Res Med Sci*. 2017;5(10):4512–8.
- Kirubahar R, Bose S, Kanna V, Murugadoss K. Comparison of clonidine and dexmedetomidine as an adjuvant to bupivacaine in supraclavicular brachial plexus block for upper limb orthopedic procedures. 2016;4:1172–6.
- Yoshitomi T, Kohjitani A, Maeda S, Higuchi H, Shimada M, Miyawaki T. Dexmedetomidine enhances the local anesthetic action of lidocaine via an α_2 A adrenoceptor. *Anesthesia & Analgesia*. 2008;107(1):96–101.
- Brummett CM, Norat MA, Palmisano JM, Lydic R. Perineural administration of dexmedetomidine in combination with bupivacaine enhances sensory and motor blockade in sciatic nerve block without inducing neurotoxicity in rat. *The Journal of the American Society of Anesthesiologists*. 2008;109(3):502–11.
- Abosedira M. Adding clonidine or dexmedetomidine to lidocaine during Bier's block: a comparative study. *J Med Sci*. 2008;8(7):660–4.
- Ammar AS, Mahmoud KM. Ultrasound-guided single injection infraclavicular brachial plexus

- block using bupivacaine alone or combined with dexmedetomidine for pain control in upper limb surgery: A prospective randomized controlled trial. *Saudi journal of anaesthesia*. 2012;6(2):109.
19. Kosugi T, Mizuta K, Fujita T, Nakashima M, Kumamoto E. High concentrations of dexmedetomidine inhibit compound action potentials in frog sciatic nerves without α_2 adrenoceptor activation. *British journal of pharmacology*. 2010;160(7):1662–76.
 20. Esmoğlu A, Mizrak A, Akin A, Turk Y, Boyacı A. Addition of dexmedetomidine to lidocaine for intravenous regional anaesthesia. *European journal of anaesthesiology*. 2005; 22(6): 447–51.
 21. 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: Official Journal of the American Association of Electrodiagnostic Medicine*. 2001;24(2):254–61.
 22. Pöpping DM, Elia N, Marret E, Wenk M, Tramer MR, Warner DS, et al. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. *The Journal of the American Society of Anesthesiologists*. 2009;111(2):406–15.
 23. Brummett CM, Hong EK, Janda AM, Amodeo FS, Lydic R. Perineural dexmedetomidine added to ropivacaine for sciatic nerve block in rats prolongs the duration of analgesia by blocking the hyperpolarization-activated cation current. *The Journal of the American Society of Anesthesiologists*. 2011;115(4):836–43.