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COMPARISON OF DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT TO BUPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

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ABSTRACT

Background and aims:-Adjuvants are often used with local anaesthetics in supraclavicular brachial plexus block(SBPB) for its synergistic effect by prolonging the duration of sensory and motor block. Alpha 2 agonists, clonidine and dexmedetomidine are combined with local anaesthetics to extend the duration of regional anaesthesia.The purpose of this study was to compare the effects of clonidine and dexmedetomidine as an adjuvant to bupivacaine(0.25%) in Supraclavicular brachial plexus block(SBPB) with respect to the hemodynamic variations;onset,duration of sensory and motor block along with duration of analgesia.

Methodology:-A randomized double blind prospective study involving 75 patients aged between 18 and 60yrs of ASA status I and II undergoing upper limb surgeries under SBPB was carried out at SMCH.The patients were randomly divided into three groups:Group B–received 35 ml of 0.25% Bupivacaine with 2ml of 0.9% normal saline, GroupC–received 35 ml of 0.25 % Bupivacaine with Clonidine 1µg/kg mixed with 0.9% normal saline to make total volume of 2ml and GroupD–received 35ml of Bupivacaine 0.25% with Dexmedetomidine 1µg/kg mixed with 0.9% normal saline to make a total volume of 2ml.Heart rate,systolic and diastolic blood pressure; onset and duration of sensory blocks, motor blocks and duration of analgesia;sedation and adverse effects,if any,were assessed.

Results: The groups were comparable with respect to age,sex,weight,ASA status and surgical characteristics.The mean onset of sensory and motor blockade and mean duration of sensory and motor blockade were faster and prolonged in Group D in comparison to Group C and Group B which were statistically highly significant($p<0.001$). Hypotension, bradycardia, sedation and decreased respiratory rate were seen in few patients in Dexmedetomidine group.

Conclusion: We conclude that dexmedetomidine can be a better alternative to clonidine when administered with Bupivacaine as an adjuvant for SBPB for upper limb surgeries.

INTRODUCTION

Regional anaesthesia presents indubitable advantages in almost all branches of surgery because it provides perfect anaesthesia and long lasting post operative analgesia. Peripheral nerve blocks are often used either as an adjuvant to general anaesthesia or as a sole anaesthetic modality by providing a good quality of analgesia, effectiveness in terms of cost, performance and margin of safety, and allowing for faster discharge from hospital.

Supraclavicular brachial plexus block provides rapid, dense anaesthesia and analgesia of entire upper extremity surgery with a complete muscular relaxation and stable intraoperative hemodynamic condition. It provides a reliable anaesthesia for upper limb surgeries by anaesthetizing the middle and lower trunk of the brachial plexus (median, radial and ulnar nerve).

Local anaesthetics administered in regional nerve blocks provides postoperative pain relief in many surgical procedures by blocking signal traffic to the dorsal horn of the spinal cord.Bupivacaine,an amide local anaesthetic agent,is frequently used in the peripheral nerve blocks to provide a longer duration of action (3 to 8hrs) and has a favourable ratio of sensory to motor neural block (1).Over the time,the adjuvants to local anaesthetic like opioids, neostigmine, hyaluronidase, midazolam, Clonidine, Dexmedetomidine, etc.(2–4) have been used to lower the dose of each agent and modify the block in terms of quick onset, good quality, prolonged duration and postoperative analgesia.

Clonidine, an alpha-2 agonist, provides analgesia by its action on presynaptic alpha-2 adrenergic receptors causing modulation of pain pathway, produces sedation through its action on pontine locus coeruleus and enhances the effect of local anaesthetics when given as an adjuvant intrathecally, epidurally and in peripheral nerve blocks(5).

Dexmedetomidine,a more selective alpha$_2$ adrenoreceptor agonist,is also used to enhance central neuraxial blockade with its more potent sedative and analgesic action, and the alpha2:alpha1 selectivity of Dexmedetomidine is eight times more than that of clonidine(6).It improves the quality of intrathecal and epidural anaesthesia and peripheral nerve blocks(7,8).

The **aim of this study** is to compare the peripheral action of dexmedetomidine and clonidine with lower concentration of bupivacaine (0.25%) to prolong the duration of block with adequate anaesthesia in supraclavicular brachial plexus block.

MATERIALS AND METHOD

A randomized double blind prospective study involving 75 patients aged between 18 and 60 years of physical status ASA I and II undergoing upper limb surgeries under supraclavicular brachial plexus block lasting for more than 30 minutes were included in the study.The study was carried out at SILCHAR MEDICAL COLLEGE AND HOSPITAL, Silchar, Assam, from June 1st, 2018 to May 31st, 2019 after obtaining Institutional Ethical Committee clearance and written informed consent from the patients.

Inclusion criteria:

1. Patients aged between 18-60 years, of both sexes.
2. Patients with ASA grade I and II, scheduled for upper limb surgeries.
3. Patients who gave informed written consent.

Exclusion criteria:

1. An allergy to local anaesthetic drug.
2. Bleeding disorder.
3. Uncontrolled diabetes mellitus, hypertension.
4. Pregnant women.
5. Pre-existing peripheral neuropathy.

On the day prior to surgery, a thorough examination of all the systems of the patients including the surface anatomy of the blocks, written informed consent, airway assessment, pre-anaesthetic preparation with overnight fasting and oral Alprazolam 0.5 mg and routine laboratory examinations during the pre-anaesthetic evaluation were undertaken.

The 75 patients were randomly allocated into three groups and each group consisted of 25 patients:

1) Bupivacaine –normal saline group (Group B)- received 35 ml of 0.25% Bupivacaine with 2ml of 0.9% normal saline,
2) Bupivacaine -clonidine group (Group C)- received 35 ml of 0.25 % Bupivacaine with Clonidine 1μg/kg mixed with 0.9% normal saline to make total volume of 2ml and
3) Bupivacaine-dexmedetomidine group (Group D)- received 35ml of Bupivacaine 0.25% with Dexmedetomidine 1μg/kg mixed with 0.9% normal saline to make a total volume of 2ml.

Identical syringes containing 1 ml of either clonidine or dexmedetomidine and labeled only with study number were prepared by an investigator neither involved in the administration of block nor following up of patients.All patients fasted for 6–8 h before surgery.All necessary equipments and drugs needed for administration of general anaesthesia and for emergency resuscitation were kept ready in order to manage failure of block or toxic reactions occurring during procedure.

Before the start of the procedure, patient's pulse rate, blood pressure, respiratory rate and saturation of oxygen were recorded. An intravenous line was secured in the unaffected limb and Ringer's lactate was started.

Under aseptic conditions, brachial plexus block was performed by supraclavicular approach with the patients placed in supine position. Neural localization was achieved by using a nerve stimulator connected to 22G,50 mm long stimulating needle (Stimuplex D; B. Braun).The position of the needle was judged adequate when an output current of 0.5 mA elicited a slight distal motor response.

After antiseptic painting and draping, a skin wheal was raised with local anaesthetic. The stimuplex needle was connected with the nerve stimulator, with the current output set at 1.0 mA and repeat twitch mode selected by the assistant under the guidance of an anaesthetist. The needle was inserted in a caudal slightly medial and posterior direction. On needle insertion, a twitch of the upper trunk (shoulder) was considered as the evidence of the needle approaching the brachial plexus. Wrist flexion and extension of the fingers were taken as acceptable responses and the current was gradually reduced between 0.2 to 0.5 mA, maintaining the visible twitches. The total volume(35ml) of the anaesthetic solution containing plain local anaesthetic or combined with clonidine or dexmedetomidine was injected at an incremental dose of 4ml each, preceded by negative aspiration for air or blood.A 3-min massage was performed to facilitate an even drug distribution.

The effects of the anaesthetic agents on the following parameters were observed:

1. The time of onset for sensory blockade, defined as time between injection and total abolition of pinprick response, was evaluated in four nerve areas (radial, ulnar, median and musculocutaneous)at every 5 minutes till 30 minutes after the injection. The block was judged to have failed if anaesthesia was not present in 2 or more peripheral nerve distributions and such patients were excluded from the study. Sensory block was assessed by pinprick test and graded as Grade 0 = no sensation felt, Grade 1 = dull sensation felt, Grade 2 = sharp pain felt.
2. The **onset time of motor blockade** was determined according to modified Bromage scale(9) for upper limb ranging from Grade 0(normal motor function) to Grade 2(complete motor block with inability to move the fingers).Following tests were done to see different nerve function:thumb abduction for the radial nerve,thumb adduction for the ulnar nerve,thumb opposition for the median nerve and flexion of elbow for the musculocutaneous nerve.Time of onset of motor block, defined as the time between injection of local anesthetic and inability to move the joints was evaluated at every 5 minutes and time to block atleast two major nerves was noted.
3. The **duration of sensory blockade**,defined as the time between onset of action and return of pinprick response,was assessed every 30 minutes in at- least 3 major nerve distributions.
4. The **duration of motor block** was assessed every 30 minutes till the return of complete muscle power in three major nerve distributions.
5. The **duration of analgesia**,defined as the time between onset of action and onset of pain,when patients received the first dose of analgesic.

During surgery arterial blood pressure,pulse,respiratory rate and peripheral oxygen saturation were monitored.No sedatives were given during surgery and degree of sedation was assessed immediately after giving the block **by using RAMSAY SEDATION SCORE**(10) .

Patients were evaluated post operatively after 2 hours,6hours,12 hours and at 24 hours for the following parameters like motor and sensory recovery, pulse rate, blood pressure, respiratory rate and any side effects like bradycardia, nausea, vomiting, drowsiness, pruritus, respiratory depression. Inj.Diclofenac Sodium 50-75mg IM was given for rescue analgesia.

Statistical Methods:

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean, SD(Min-Max) and results on categorical measurements are presented in Number (%).Significance is assessed at 5% level of significance.

ANOVA(Analysis of variance) and Tukey test (Post hoc analysis test) had been used to find the significance of study parameters on continuous scale among three groups (Inter group analysis)on metric parameters and on categorical scale between the groups respectively.

The p value <0.05 was considered Statistically significant.

The Statistical software, **GRAPHPAD INSAT-3,** was used for the analysis of the data and Microsoft word and Excel had been used to generate graphs, tables etc**.**

RESULTS

The mean age, weight, sex distribution, ASA grading and duration of surgery among the three groups were comparable. There was no significant difference amongst the groups with regard to demographic variables(p-value>0.05).

Onset of sensory blockade(loss of sensation to pinprick)and motor blockade (paralysis of upper limb)were faster in Group D(6.52±1.05min and 8.36±0.95min respectively)as compared to Group C(8.92±1.0min and 10.76±1.05min respectively) and Group B(14.84±1.93min and 17.00±2.18min respectively).These differences were statistically highly significant($p \leq 0.001$).

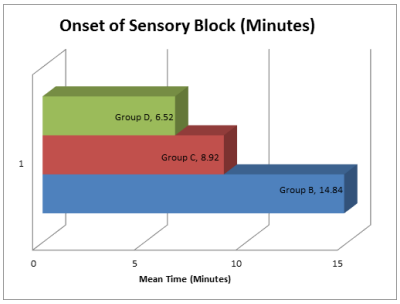

Figure 1: Comparing The Mean Time (minutes) Of Onset Of Sensory Block

Table 1 :Sensory and motor block onset time, block and analgesia durations in all three groups

	Group B	Group C	Group D	P value
Onset (sensory)	14.84±1.93	8.92±1.0	6.52±1.05	<0.001
Onset (motor)	17.00±2.18	10.76±1.05	8.36±0.95	<0.001
Duration (sensory)	4.94±0.59	7.56±0.39	10.72±0.85	<0.001
Duration (motor)	5.94±0.47	9.24±0.97	12.99±0.65	<0.001
Duration of analgesia	5.17±0.56	8.66±0.51	12.27±0.63	<0.001

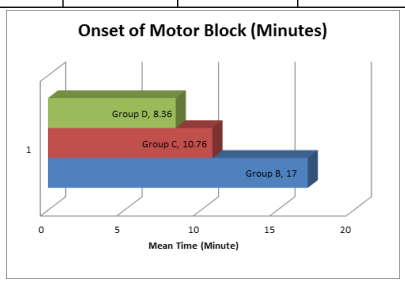

Figure 2: Comparing The Mean Time (minutes) Of Onset Of Motor Block

The mean duration of sensory blockade and motor blockade were maximal in Group D(10.72±0.85hrs and 12.99±0.65hrs respectively)as compared to Group C(7.56±0.39hrs and 9.24±0.57hrs respectively)and Group B(4.94±0.59hrs and 5.94±0.47hrs respectively).These differences were statistically highly significant(p≤0.001).

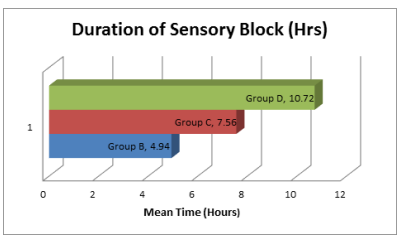

Figure 3: Comparing The Mean Time (hrs) Of Duration Of Sensory Block

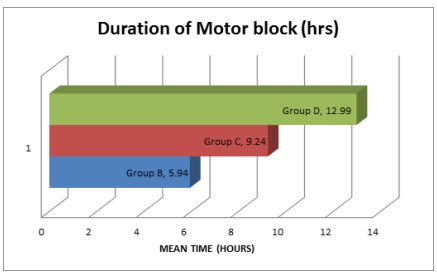

Figure 4: Comparing The Mean Time (hrs) Of Duration Of Motor Block

The mean duration of analgesia was maximum in Group D(12.27±0.63hrs) as compared to Group C(8.66±0.51hrs)and Group B(5.17±0.56hrs).This difference was statistically highly significant(p≤0.001).

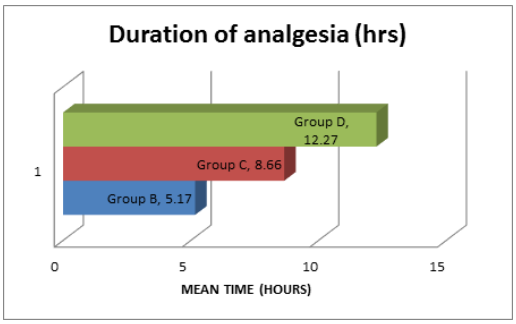

Figure 5: Comparing The Mean Time (hrs) Of Duration Of Analgesia Among The Three Groups

The mean heart rate ranged from 76.88±8.20 to 78.88±9.34 beats per min in Group B,from 74.32±5.45 to 81.48±7.81 beats per min in Group C and from 72.64±8.42 to 80.96±8.72 beats per min in Group D.The statistical analysis by ANOVA test had shown that there was no significant difference in heart rate among the three groups(p>0.05).

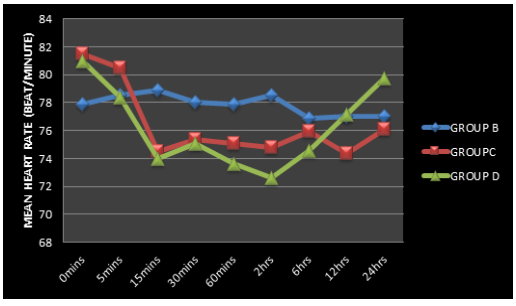

Figure 6: Comparison Of Heart Rate At Different Time Interval Among The Groups

The mean systolic blood pressure ranged from 122.24±9.76 to 117.44±8.03 mm of Hg in Group B,from 124.44±7.22 to 111.40± 6.47 mm of Hg in Group C and from 126.72±8.01 to 106.24±7.07mm Hg in Group D.The statistical analysis by ANOVA showed that there was highly significant fall of systolic blood pressure in 60th min and in 2nd hour among the three groups(p<0.001).

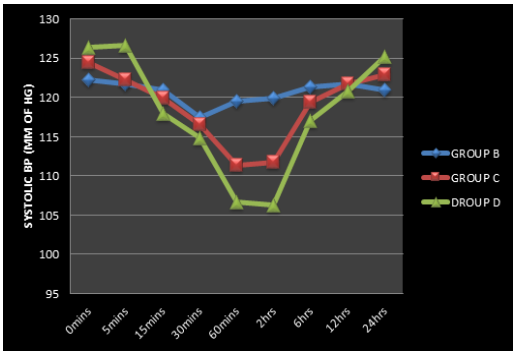

Figure 7: Comparison Of Systolic Blood Pressure Among The Groups.

The mean diastolic blood pressure ranged from 77.68±9.30 to 75.12±8.47 mm of Hg in Group B,from 79.04±7.23 to 62.20±3.19 mm of Hg in Group C and from 74.64±9.32 to 60.96±5.86 mmHg in Group D.The statistical analysis by ANOVA showed that there was highly significant fall of diastolic blood pressure in 60th min and in 2nd hour among the groups(p ≤0.001).

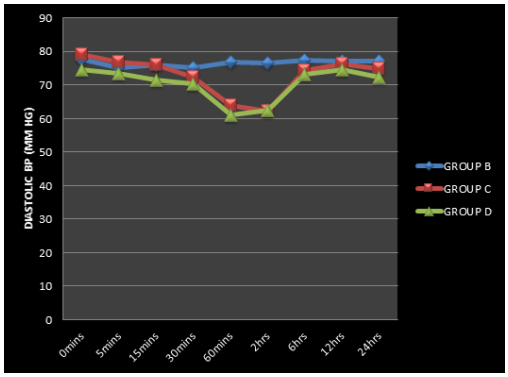

Figure 8: Comparison Of Diastolic Blood Pressure Among The Groups:

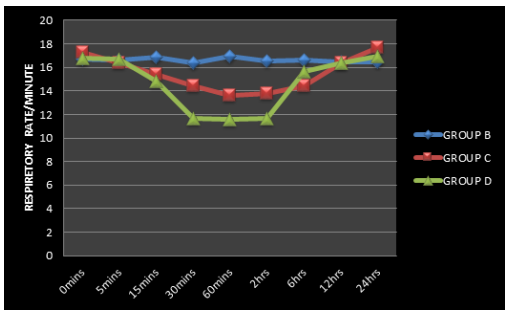

Figure 9 : Comparison Of Respiratory Rate Among The Groups

The statistical analysis by ANOVA showed that there was highly significant difference in respiratory rate in 60thmins and in 2ndhr among the groups.($p \leq 0.001$).

Only one patient had hypotension in Group B,two patients had bradycardia in Group C,and four patients had hypotension,three patients had bradycardia and another three had both hypotension and bradycardia in Group D.Statistical analysis had shown significant p value(<0.05) when compared among the three groups.

DISCUSSION

The alleviation of the pain is a primary concern of the anaesthesiologist. It has been emphasized that anaesthetic technique should be designed in such a way that it will provide residual analgesia in the postoperative period so that immediate postoperative period would be pain free.

Peripheral nerve block administered with local anaesthetic drugs alone produces analgesia limited to the duration of action of the local anaesthetic.In an attempt to enhance the perioperative analgesia,a variety of adjuncts such as opioids, verapamil,neostigmine,tramadol and alpha2 agonists like clonidine have been administered into the brachial plexus sheath in conjunction with local anaesthetics.These adjuncts may not only prolong the analgesic duration but also thought to reduce the systemic analgesic consumption as well as their side effects.

Kosugi *et al*.,examined the effects of various adrenoceptor agonists including dexmedetomidine, tetracaine, oxymetazoline and clonidine, and also an α2 adrenoceptor antagonist(atipamezole) on compound action potential (CAP) recorded from frog sciatic nerve,and found that CAPs were inhibited by α2 adrenoceptor agents so that they were able to block nerve conduction.–(11)

Clonidine and dexmedetomidine, partial and selective alpha 2 agonists respectively are being studied and used in regional anaesthesia practice as adjuvant to local anaesthetic agents for a long period of time. Widespread presence of alpha 2 receptors in brain,spinal lamina and peripheral nerves and their role in pain modulation explains the analgesic and local anaesthesia sparing action of these agents.

Clonidine enhances both sensory and motor blockade of neuraxial and peripheral nerves after injection of local anaesthetic solutions–(12) by four proposed mechanisms. These mechanisms are centrally mediated analgesia, alpha-2-adrenoreceptor mediated vasoconstriction, attenuation of inflammatory response and direct action on peripheral nerves(13). Clonidine possibly enhances or amplifies the sodium channel blocking action of local anesthetics by opening up the potassium channels resulting in hyperpolarization,a state in which the cell is unresponsive to excitatory input.–(14)

Dexmedetomidine, a more selective alpha 2 agonist is used in humans through intravenous and combined use with local anaesthetic agents as an adjunct to neuraxial and perineurally administered local anaesthetic agents. Dexmedetomidine, a selective α2 adrenoceptor agonist has an α2:α1 binding selectivity ratio of 1620:1 as compared to 220:1 for clonidine,thus decreasing the unwanted side effects of α1 receptors.(15,16) The hypothesized mechanisms of dexmedetomidine administration in the peripheral nerve block are as follows: Dexmedetomidine inhibits the function of sodium channels and neuronal potassium current–(17,18)and blocks the hyperpolarization-activated cyclic nucleotide-gated channels, resulting in the enhancement of activity-dependent hyperpolarization and leading to the inhibition of substance *P* release in the nociceptive pathway at the dorsal root neuron.–(19)

In the study of **Eledjam JJ et al**,clonidine 150µg was added to 40 ml of 0.25% bupivacaine to find the efficacy of α2 agonist on brachial plexus block–(9).**Swamy et al** added 1µg/kg of either clonidine or dexmedetomidine to bupivacaine 0.25%(35 cc)to compare their efficacy on supraclavicular brachial plexus block study (20). **Rao et al** added 1µg/kg of either clonidine or dexmedetomidine to bupivacaine 0.25%(38 cc) to compare their efficacy on supraclavicular brachial plexus block–(21). Therefore,we decided to use 1 µg/kg of clonidine or dexmedetomidine added to 35 ml of 0.25% bupivacaine to compare their efficacy on brachial plexus block.

In our study,premedication and anaesthetic techniques were kept constant, excluding any variation in responses due to a variety of drugs and techniques.

Kirubahar *et al.*,evaluated the effect of 2µgm/kg each of dexmedetomidine and clonidine as adjuvants to 35 ml of 0.375%bupivacaine for supraclavicular brachial plexus block in upper limb surgeries and found that the onset of sensory and motor block was faster in dexmedetomidine than clonidine–(22).Similar observations were made by **Kakad et al (23) and Sebastian D et al(24).**While on the other hand,in our study clonidine also had faster onset of sensory and motor block than the control group which came into agreement with **Singh S *et al* and Chakrabarty et al**.(25)

In our study,it was observed that there was significant increase in mean duration of sensory and motor block in both group C and group D;more with the addition of dexmedetomidine in comparison to clonidine and control group.This prolonged duration of sensory and motor blockade following the addition of clonidine and dexmedetomidine to local anaesthetics in peripheral nerve blocks has also been reported in earlier studies by Tripathi A et al and Sebastian D et al.

There was significant decrease in analgesic consumption in the postoperative period with the use of adjuvants dexmedetomidine and clonidine.

In accordance with study by Swami *et al*. and Gandhi R et al(26),in our study no significant serious side effects were reported in any group except for lower pulse rates and blood pressures observed in dexmedetomidine groups that were managed conservatively. Various authors reported significant sedation with the use of clonidine and dexmedetomidine corroborating the results of our study.

In our study, we observed strong association of depression of respiratory rate in Dexmedetomidine group in comparison to Clonidine group and control group. We did not find any appropriate study to compare changes in respiratory rate.

Our study design had an inherent advantage, that only brachial plexus block was used for all the patients and no other analgesic was given intra operatively to avoid influences of other drugs on our study drugs. The major limitation of our study was that we did not perform ultrasound-guided blocks because of unavailability at the time of our study; which could have helped us to lower dosages and volumes of local anaesthetic. While finally, the small sample size in each group might have limited the true clinical significance of our comparison.

CONCLUSION:

Therefore, we have observed that dexmedetomidine hastens the onset of sensory and motor block, prolongs the duration of sensorimotor blockade, prolongs the duration of analgesia and decreases analgesic consumption in the post- operative period.

So, we can conclude that Dexmedetomidine can be a better alternative to clonidine when administered with Bupivacaine as an adjuvant for supraclavicular brachial plexus block for upper limb surgeries.

REFERENCES

1. De Jong R.Regional anaesthesia and analgesia.Philadelphia, Pa:Saunders;1996.Local anesthetic pharmacology.In Brown DL,ed; pp.124–42.
2. Bazin JE,Massoni C,Bruelle P,Fenies V,Groslier D,Schoeffler P.The addition of opioids to local anaesthetics in brachial plexus block: the comparative effects of morphine, buprenorphine and sufentanil. Anaesthesia.1997;52(9):858–862.
3. Bone HG,Van Aken H, Booke M,Bürkle H.Enhancement of axillary brachial plexus block anesthesia by coadministration of neostigmine.Reg Anesth Pain Med. 1999;24(5):405–410.
4. Keeler JF,Simpson KH, Ellis FR, Kay SP.Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block.BJA Br J Anaesth.1992;68(1):68–71.
5. JC Eisenach, M De Kock, W Klimscha 2-Adrenergic agonists for regional anesthesia Anesthesiology,85 (1996), pp. 655-674
6. Virtanen R, Savola JM, Saano V, Nyman L.Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist.Eur J Pharmacol. 1988 May 20;150(1–2):9–14.
7. Obayah GM, Refaie A, Aboushanab O, Ibraheem N, Abdelazees M.Addition of dexmedetomidine to bupivacaine for greater palatine nerve block prolongs postoperative analgesia after cleft palate repair.Eur J Anaesthesiol EJA.2010;27(3):280–284.
8. Rancourt M-PM, Albert NT, Côté M, Létourneau D-R, Bernard P-M.Posterior tibial nerve sensory blockade duration prolonged by adding dexmedetomidine to ropivacaine.Anesth Analg.2012;115(4):958–962.
9. Eledjam JJ, Deschodt J, Viel EJ, Lubrano JF, Charavel P, d'Athis F, et al.Brachial plexus block with bupivacaine:effects of added alpha-adrenergic agonists:comparison between clonidine and epinephrine.Can J Anaesth.1991;38(7):870–875.
10. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R.Controlled sedation with alphaxalone-alphadolone.Br Med J.1974;2(5920):656–659.
11. Kosugi T, Mizuta K, Fujita T, Nakashima M, Kumamoto E.High concentrations of dexmedetomidine inhibit compound action potentials in frog sciatic nerves without 2 adrenoceptor activation.Br J Pharmacol.2010;160(7):1662–1676.
12. El-Hennawy AM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS, Boulis SR. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth.2009;103(2):268–274.
13. Brummett CM, Amodeo FS, Janda AM, Padda AK, Lydic R.Perineural dexmedetomidine provides an increased duration of analgesia to a thermal stimulus when compared with a systemic control in a rat sciatic nerve block.2010;
14. Strichartz GR.The alpha 2-adrenergic agonists clonidine and guanfacine produce tonic and phasic block of conduction in rat sciatic nerve fibers.Anesth Analg.1993;76:295–301.
15. Gaumann D, Forster A, Griessen M, Habre W, Poinsot O, Santa Della D.Comparison between clonidine and epinephrine admixture to lidocaine in brachial plexus block.Anesth Analg.1992;75(1):69–74.
16. Gaumann DM, Brunet PC, Jirounek P. Clonidine enhances the effects of lidocaine on C-fiber action potential.Anesth Analg. 1992;74(5):719–725.
17. Chen B-S, Peng H, Wu S-N. Dexmedetomidine, an 2-adrenergic agonist, inhibits neuronal delayed-rectifier potassium current and sodium current.Br J Anaesth. 2009;103(2):244–254.
18. Maruta T, Nemoto T, Satoh S, Kanai T, Yanagita T, Wada A, et al. Dexmedetomidine and clonidine inhibit the function of Na v 1.7 independent of 2-adrenoceptor in adrenal chromaffin cells.J Anesth. 2011;25(4):549.
19. Guo T-Z, Jiang J-Y, Buttermann AE, Maze M.Dexmedetomidine injection into the locus ceruleus produces antinociception. Anesthesiology. 1996;84(4):873–881.
20. Swami SS, Keniya VM, Ladi SD, Rao R.Comparison of dexmedetomidine and clonidine (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.
21. Rao KG, Kapoor P, Chaurasiya MK, Shukla A.A randomised double blind prospective study to compare clonidine and dexmedetomidine as an adjuvant in supra-clavicular brachial plexus block. Indian J Fundam Appl Life Sci. 2014;4:226–29.
22. Kirubahar R, Sundari B, Kanna V. Comparison of clonidine and dexmedetomidine as an adjuvant to bupivacaine in supraclavicular brachial plexus block for upper limb orthopedic procedures. Int J Res Med Sci. 2016;4:1172–1176.
23. Kakad R, Chaudhari D, Lawhale S, Ghodki SG, Bite BM.Comparative study between dexmedetomidine and clonidine as an adjunct to bupivacaine in brachial plexus block in orthopaedic surgeries. J Contemp Med Dent. 2015;3:39–43.
24. Sebastian D, Ravi M, Dinesh K, Somasekharam P.Comparison of dexmedetomidine and clonidine as adjuvant to ropivacaine in supraclavicular brachial plexus nerve blocks. IOSR J Dent Med Sci. 2015;14:91–97.
25. Chakraborty S, Chakrabarti J, Mandal MC, Hazra A, Das S.Effect of clonidine as adjuvant in bupivacaine-induced supraclavicular brachial plexus block:A randomized controlled trial.Indian J Pharmacol.2010;42(2):74.
26. Gandhi R, Shah A, Patel I.Use of dexmedetomidine along with bupivacaine for brachial plexus block.Natl J Med Res. 2012;2(1):67–9.