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CLONIDINE AND DEXMEDETOMIDINE AS ADJUVANT TO BUPIVACAINE, A LOCAL ANAESTHETIC, IN INTERSCALENE BRACHIAL PLEXUS BLOCK-A COMPARATIVE STUDY

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ABSTRACT

The aim of study is to compare Clonidine and Dexmedetomidine – both alpha 2 agonists, added to local anaesthetic to prolong the duration of neuraxial block and peripheral nerve block. We have in this study compared both the drugs separately and individually as an adjuvant to bupivacaine hydrochloride in interscalene brachial plexus block with regards to onset and prolongation of duration of sensory and motor blockage. It is found in our study that Dexmedetomidine in comparison to clonidine when added to local anaesthetic Bupivacaine, in interscalene Brachial plexus block, much enhanced the duration of sensory, motor block and there was more prolongation of post-operative analgesia. It also enhanced the quality of block compared to clonidine

INTRODUCTION

Brachial Plexus Block is nowadays standard protocol for upper limb surgeries instead of general anaesthesia. Adjuvants like alpha 2 agonists are added to prolong the duration of peripheral nerve block, both sensory and motor and also considerably prolongs duration of post-operative analgesia.

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 use the alpha2 adrenergic agents, dexmedetomidine and clonidine. In clinical practice with success.

Alpha-2 adrenergic receptor agonists have been the focus of interest for their sedative, analgesic, perioperative sympat holytic and cardiovascular stabilizing effects with reduced anaesthetic 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 anaesthesia. Dexmedetomidine, a potent alpha2 adrenoceptor agonist, is approximately eight-times more selective towards the alpha2 adrenoceptor than clonidine. In previous clinical studies, intravenous dexmedetomidine resulted in significant opioid sparing effects as well as a decrease in inhalational anaesthetic requirements. In various animal studies, dexmedetomidine has been reported to enhance sensory and motor blockade along with increased duration of analgesia. In humans, dexmedetomidine has also shown to prolong the duration of block and post-operative analgesia when added to Iocal anaesthetic in various regional blocks. The current study was designed to test the hypothesis that dexmedetomidine when added as an adjuvant to local anaesthetic in interscalene brachial plexus block enhanced the duration of sensory and motor block, duration of analgesia and quality. of block as compared with clonidine.

METHODS

After ethical committee approval and written informed consent, a double-blind randomized prospective clinical study was carried out on 80 American Society of Anaesthesiologist (ASA) Grade I and II patients of either sex, aged 18-60 years, undergoing various orthopaedic surgeries on the upper limb under interscalene brachial plexus block. The study was conducted in two groups of 40 patients each. The patients were randomly assigned using "slips in a box technique" to one of the following groups:

Group C: Bupivacaine 0.25% [30 cc) + clonidine 0.75micro gram\kg

Group D: Bupivacaine 0.25% (30 cc) + dexmedetomidine 0.50microgram\kg

Patients on adrenoreceptor agonist or antagonist therapy, with known hypersensitivity to local anaesthetic drugs, bleeding disorders, uncontrolled diabetes mellitus, pregnant women and pre-existing peripheral neuropathy, were exclud ed from the study.

On arrival in the operation room, baseline heart rate, blood pressure and oxygen saturation were recorded. An intravenous line was secured in the unaffected limb and Ringer's lactate was started.

AII the patients received brachial plexus block through the interscalene approach by an experienced anaesthesiologist different from the one assessing the patient intra- and post-operatively. Both were blinded to the treatment groups. Neural localization was achieved by using a nerve locator (Fisher and Paykel, New Zealand) connected to a22 G, 5O-mm-long stimulating needle [Stimuplex, Braun, Germany). The Iocation end point was a distal motor response with an output lower than 0.5 mA in the median nerve region.

Following negative aspiration, 30 mL of a solution containing local anaesthetic combined with clonidine or dexmed etomidine as mentioned above was injected. Through interscalene brachial plexus route.

Sensory block was assessed by the pin prick method. Assessment of sensory, block was done at each minute after completion of drug injection in the dermatomal areas corresponding to median nerve, radial nerve, ulnar nerve and musculocutaneous nerve till complete sensory blockade. Sensory onset was considered when there was a dull sensation to pin prick along the distribution of any of the above-mentioned nerves.

Complete sensory block was considered when there was complete loss of sensation to pin prick.

Sensory block was graded as-
Grade 0: Sharp pin felt
Grade 1: Analgesia, dull sensation felt
Grade 2: Anaesthesia. no sensation felt.

Assessment of motor block was carried out by the same observer at each minute till complete motor blockade after drug injection. Onset of motor blockade was considered when there was Grade 1 motor blockade.

Peak motor block was considered when there was Grade 2 motor blockade. Motor block was determined according to a modified Bromage scale for upper extremities on a 3-point scale.

Grade 0: Normal motor function with full flexion and extension of elbow, wrist and fingers

Grade 1: Decreased motor strength with ability to move the fingers only
Grade 2: Complete motor block with inability to move the fingers.

The block was considered incomplete when any of the segments supplied by median, radial, ulnar and musculocutaneous nerve did not have analgesia even after 30 min of drug injection. These patients were supplemented with intravenous fentanyl (1microgram\kg) and midazolam (0.10mg\kg). When more than one nerve remained unaffected, it was considered failed block. In this case, general anaesthesia was given intraoperatively. Patients were monitored for haemodynamic variables such as heart rate, blood pressure and oxygen saturation every 5 min after the block intraoperatively and every 30 min post-operatively. Sedation of patient was assessed by the Ramsay Sedation Score. At the end of the procedure, quality of operative conditions was assessed according to the following numeric scale:

Grade 4: (Excellent)No complaint from patient
Grade 3:(Good) Minor complaint with no need for the supplemental analgesics
Grade 2:(Moderate) Complaint that required supplemental analgesia
Grade 1:(Unsuccessful)Patient given General anaesthesia

Assessment of blood loss was done and fluid was administ ered as per the loss. Duration of surgery was noted.

The intra- and post-operative assessment was done by an anaesthesiologist who was unaware of the drug used. Patients were assessed for duration of analgesia as per a numeric rating scale of 0 to 10. The numeric rating scale was recorded post-operatively 'every' 60 min till the score of 5. The rescue analgesia was given in the form of inj. diclofenac sodium (1.5 mg/ kg) intramuscularly at the Numeric Rating Scale of 5 and the time of administration was noted. All patients were observed for any side-effects like nausea, vomiting, dryness of mouth and complications like pneumothorax, haematoma, local anaesthetic toxicity and post-block neuropathy in the intra- and post-operative periods.

The duration of sensory block was defined as the time interval between the end of local anaesthetic administration and the complete resolution of anaesthesia on all nerves. The duration of motor block was defined as the time interval between the end of local anaesthetic administration and the recovery of complete motor function of the hand and forearm.

Statistical analysis

The data was analysed by SPSS version (Statistical Package for Social Sciences) software. Unpaired t-test was applied for demographic data, haemodynamic parameters, onset and duration of sensory and motor blockade and duration of analgesia. Fisher exact test was applied for assessment of quality of block. P-value was considered significant if <0.05 and highly significant if <0.001.

RESULTS

Hundred patients posted for upper limb surgeries were assessed for suitability to enrol in the study. Seven patients declined to participate in the study, 'Five patients were excluded as they 'were posted for soft tissue surgeries of the upper limb. Eight patients were excluded as they 'were found to be on beta blockers. anticoagulation drugs and had uncontrolled diabetes mellitus. The remaining 80 patients fulfilling the inclusion criteria were randomly assigned to one of the two groups. There was no protocol deviation pre operatively, except for one patient in group C who had to be given general anaesthesia for inadequate block.

Both groups were comparable in terms of age, gender, weight and type of surgery. [Table 1] (p> 0.001)

Table 1 : Patient Characteristics

Parameters	Group C (Mean ± SD)	Group D (Mean ± SD)	P value
Age(years)	33.73 ± 12.09	33.83 ± 16.78	NS
Weight(kg)	58.4 ± 4.3	54.30 ± 8.11	NS
Gender (M/F)	22/8	19/11	NS
Type of Surgeries			
#Olecranon	12	13	
#Lower end humerus	11	8	
#Radius ulna	7	9	

The baseline haemodynamic parameters were comparable in both groups. Significantly lower pulse rate was observed, at 60, 90 and 120 min, but not less than 60 beats/min, in Group D as compared with Group C[P<0'001). Systolic and diastolic blood pressure were found to be significantly lower than baseline from 30 to 120 min in Group D as compared with Group C (P<0'001). No treatment was required for this fall in blood pressure. The haemodynamic parameters were comparable atthe end of 180 min.

Onset of sensory block was faster in Group D than in Group C, while onset of motor block was faster in Group C than in Group D, but the difference was not statistically significant [Table 2] (P>0'001).

Duration of sensory block was 227.00±148.36 min in Group C as compared with 413.97± 87.31 min in group D. Statistically significant longer duration of sensory block was observed in Group D [Table 2] (P:0.0011).

The duration of motor block was 292.67±59.13 min in Group C as compared with 472.24 ± 90.06 min in Group D. Again, duration of motor block was significantly longer in Group D [Table 2] (P:0.001).

There was significant increase in duration of analgesia in Group D {456.12 ± 97.99 min) as compared to with Group C (289.67 ± 62.50). The difference was statistically significant [Table 2] (P:0.001)

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

Parameters	Group C (Mean ± SD)	Group D (Mean ± SD)	P value
Onset time of sensory block (min)	2.33 ± 1.21	1.77 ± 1.28	0.083
Onset time of motor block (min)	3.87 ± 1.78	4.65 ± 2.46	0.162
Duration of sensory block (min)	227.00 ± 48.36	413.97 ± 87.31	0.001
Duration of motor block (min)	292.67 ± 59.13	472.24 ± 90.06	0.001
Duration of analgesia (min)	289.67 ± 62.50	456.21 ± 97.99	0.001

In Group D, 80% of the patients achieved Grade IV quality of block as opposed to 4o% in Group C(P<0.05). There were a total17 patients in Group C with Grade II and III block and six patients in Group D who required sedation or sedation with analgesia. One patient in Group C required general anaesthesia as the block was inadequate [Table 3].

Table 3 : Quality of block

Grade	Group C,N(%)	Group D,N(%)	*P value*
I	1 (3.3)	-	0.015
II	8(26.7)	2(6.7)	
III	9(30)	4(13.3)	
IV	12(40)	24(80)	

No side-effects (nausea, vomiting, dry mouth) were reported during the first 24 h in the post-operative period in both the groups.

DISCUSSION

In this randomized, double-blinded trial, we compared dexmedetomidine and clonidine (alpha 2 agonist) as an adjuvant to Bupivacaine in interscalene brachial plexus block, and found that there was a significantly increased duration of sensory and motor blockade in the dexmedetomidine group than in the clonidine group without any adverse effects.

Action of clonidine and dexmedetomidine:

Clonidine was initially used for its antihypertensive properties, the central actions are mediated throughalpha2, adrenoceptors, which are situated at locus coeruleus and dorsal horn of spinal cord. But, specific peripheral effects of clonidine appear to be less obvious becausealpha2, adrenoceptors are not present on the axon of the normal peripheral nerve. There have been four proposed mechanisms for the action of clonidine in peripheral nerve blocks. These mechanisms are centrally mediated analgesia, alpha2\ adrenoceptor-mediated vasoconstrictive effects, attenuation of frog sciatic nerves action potential without alpha2, adrenoceptor activation, inflammatory response and direct action on peripheral nerve. The direct action of clonidine on the nerve, the peak amplitude of Compound action potential, can be explained on the basis of a study conducted by concentration- dependent manner.

Kosugi et al. examined the effects of various adrenoceptor agonists including dexmedetomidine, tetracaine, oxymetazoline and clonidine, and also an & alpha 2 adrenoceptor antagonist (atipamezole) on compound action potential (CAP)recorded from frog sciatic nerve, and found that CAPs were inhibited by alpha2, adrenoceptor agents so that they are able to block nerve conduction. In their meta-analysis of randomized trials showed that the beneficial effect of clonidine on the duration of analgesia was observed with all tested local anaesthetics. They observed that the prolong ation of motor block was higher when clonidine was added to bupivacaine as compared with ropivacaine. The least effect was noted with prilocaine. Dexmedetomidine and clonidine are both alpha2, selective agonists. It is possible that they work in a similar manner and may indicate a class effect.

A study by Brumett et al. showed that dexmedetomidine enhances duration of bupivacaine anaesthesia and analgesia of sciatic nerve block in rats without any damage to the nerve. The histopathological evaluation of these nerve axons and myelin sheath normal in both control and dexmedetomidine + bupivacaine groups.

In an another study, perineural dexmedetomidine added to ropivacaine for sciatic nerve block in rats prolonged the duration of analgesia by blocking the hyperpolarisation-activated cation. This effect was reversed by a hyperpo larisation-activated cation channel enhancer but not by an alpha, adrenoreceptor antagonist. This shows that the analg esic effect of peripheral perineural dexmedetomidine was caused by enhancement of the hyperpolarisation-activated cation current, which prevents the nerve from returning from a hyperpolarized state to resting membrane potential for subsequent firing. Kousugi et al. in their study found that high concentrations of dexmedetomidine inhibit CAPs in reduced the CAP peak amplitude. Clonidine and oxymetazoline, two other, agonists, also inhibit CAPs. On the other hand, adrenaline, noradrenaline and alpha, agonist phenylephrine and beta agonist isoprenaline had no effect on CAP.

Singelyn e t al. reported that a minimum dose of clonidine (0.5 microgram\kg) added to mepivacaine prolongs the duration of anaesthesia and analgesia after brachial plexus block. No added benefits were found with doses exceeding 1.5 microgram\kg The enhancing effect of a small dose of clonidine on lignocaine may be because of the evoked inhibition of C-fibre action potential. Therefore, we decided to use clonidine at a dose of 0.75microgram\kg. in our study.

In our study, we compared the addition of clonidine (Group C) at dose 0.75 microgram]kg and dexmedetomidine [Group D] 0.50 micro gram per kg to bupivacaine in interscalene brachial plexus block. The result of our study that aII patients in both groups were comparable with respect to demographic profile, duration of surgery and type of surgery. With these doses, we found stable haemodynamic in patients except significant lower pulse rate in Group D at 60, 90 and 120 min as compared with Group C, but not less than 60 beats/ min.

The concern of prolongation of motor block was minimal on patient discomfort on movement in the post-operative period. Memis et al. in their study showed that addition of dexmedetomidine to lignocaine for intravenous regional anaesthesia improves both the quality of anaesthesia as well as intraoperative and post- operative analgesia. In our study, the quality of block in 8O% of the patients in Group D was grade iv! i.e. excellent block without any supplementary sedation or analgesia, while 40o/o in Group C achieved grade IV quality. This improved quality of block might be the result of various mechanisms of nerve conduction block such as hyperpolarisation, and inhibition of voltage gate of sodium pump.

None of the patients in Group D required sedation intraoperatively and they were comfortable throughout the surgery with arousable sedative effects, this can be explained on the basis that some amount of systemic absorption of drug could be present. As an alpha 2, agonists produce sedation by central action, they produce inhibition of substance P release in the nociceptive pathway at the level of the dorsal root neuron and by activation of u adrenoreceptor in locus cereleus.

From this study, we would like to suggest that both clonidine and dexmedetomidine can be safely used with local anaesthetic in peripheral nerve blocks; however, duration of block with dexmedetomidine is longer

CONCLUSION

To conclude, we would like to state that dexmedetomidine prolongs the duration of sensory and motor block and enhances the quality of block as compared with clonidine when used as an adjuvant to Bupivacaine in peripheral nerve block.

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