

ORIGINAL RESEARCH

Dexmedetomidine vs clonidine as an adjuvant to bupivacaine: A comparative study to assess the motor and sensory blockade, duration of analgesia, and the intraoperative hemodynamic profile of patients**¹Dr. Ashok Das, ²Dr. Sankar Pal, ³Dr. Manas Karmakar, ⁴Dr. Jatisankar Rudra**^{1,3}Associate Professor, ²Assistant Professor, Department of Anaesthesiology, ESI-PGIMSR, Joka, Kolkata, West Bengal, India⁴Professor and Ex-HOD, Department of Anaesthesiology, Calcutta National Medical College, Kolkata, West Bengal, India**Corresponding Author**

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Received: 07 February, 2023

Accepted: 12 March, 2023

Abstract

Background: Clonidine and dexmedetomidine have been repeatedly demonstrated to prolong sensory and motor block when used intrathecally with local anaesthetics. Clonidine and dexmedetomidine have also been known to affect blood pressure in a complex fashion after intrathecal administration, because of opposing actions at multiple sites. The present study was planned to compare the effects of dexmedetomidine and clonidine on duration of analgesia, motor and sensory blockade and the intraoperative hemodynamic profile when used as an adjuvant to bupivacaine.

Methods: This was a unicentric prospective randomized, single blinded, observational study done in Department of Anaesthesiology, Calcutta National Medical College in association with Urology, orthopaedic and gynaecology & obstetrics during February, 2012 to March, 2013. Groups were designated according to the study drug received, as follows: Group D- received 2.6 ml of hyperbaric bupivacaine (13 mg) and 5 µg of dexmedetomidine (0.05 ml) and 0.35 ml of normal saline and Group C- received 2.6 ml of hyperbaric bupivacaine (13 mg), 37.5 µg of clonidine (0.25ml) and 0.15 ml normal saline. Any incidence of adverse effects in the intraoperative or immediate postoperative period were noted and again patients were followed up at 24 hours in the ward for incidence of nausea, vomiting or any other adverse reaction.

Results: In our study, maximum surgery performed were lower limb orthopaedic surgery (35%), then TURP (23.33%), then vaginal hysterectomy (21.66%) and total abdominal hysterectomy (20%). In group-C patients time for 2 segment regression was 125.5±13.35 minutes and in group-D patients higher (157±11.64 minutes). So, it can be said that both clonidine and dexmedetomidine prolongs the 2-segment regression time but dexmedetomidine is superior in prolonging 2 segment regression time. In group-C patients S1 regression time was 247.5±23.22 minutes and in group-D patients higher (303±25.66 minutes). So, it can be said that both clonidine and dexmedetomidine prolongs the time for regression to S1 level but dexmedetomidine is better alternative in prolonging the time for regression to S1 level. Group-C patients took 217.5±23.55 minutes to regain Bromage score 0

and group-D patients took 260.5 ± 20.27 minutes. So, motor blockade was also prolonged in dexmedetomidine group than in clonidine group.

Conclusion: In equipotent doses dexmedetomidine is more effective as intrathecal adjuvant to hyperbaric bupivacaine than clonidine. Neither clonidine nor dexmedetomidine increases side-effects of spinally administered hyperbaric bupivacaine if given in appropriate doses.

Keywords: Dexmedetomidine, Clonidine, Bupivacaine, Analgesia, Surgery

Introduction

Lower limb and lower abdominal surgeries can be done under general anaesthesia as well as central neuraxial block or local nerve block. However central neuraxial block especially subarachnoid block has gained popularity because of its ease of administration, high success rates, ability to provide good operative conditions, quick onset and better muscle relaxation [1].

Spinal anaesthesia with local anaesthetic alone has a short duration of action. The short duration of action creates lots of difficulties for surgeons, anaesthesiologist and the patient as duration of spinal anaesthesia sometimes falls short than the duration of surgery. It limits the type of surgeries that can be performed with spinal anaesthesia. Many a time it also warrants conversion to general anaesthesia midway between surgeries due to wearing off of the effect of spinal anaesthesia. Moreover, early analgesic intervention is required to manage postoperative pain control after spinal anaesthesia with local anaesthetics alone.

Hence number of adjuvants, such as clonidine, dexmedetomidine, midazolam, opioids, neostigmine and magnesium sulphate has been studied to prolong the effect of spinal anaesthesia [2,3]. Adjuvants are added to increase the duration and density of block but they are not free from side effects. For example, opioids cause pruritus, respiratory depression, urinary retention [4] and neostigmine produces severe nausea & vomiting and pruritus [5]. So, the search goes on for a better intrathecal adjuvant.

Clonidine, a centrally acting selective partial α_2 adrenergic agonist (220:1 α_2 to α_1) [6], is used as an intrathecal adjuvant for quite some time now. Dexmedetomidine, a highly selective, specific, and potent α_2 adrenergic agonist (1620:1 α_2 to α_1) [7], has come into use in recent times. Clonidine and dexmedetomidine have been repeatedly demonstrated to prolong sensory and motor block when used intrathecally with local anaesthetics [2,3,8].

Clonidine and dexmedetomidine have also been known to affect blood pressure in a complex fashion after intrathecal administration, because of opposing actions at multiple sites.

The addition of clonidine or dexmedetomidine also allows for a reduction in the total dose of the local anaesthetic used, which translates into better hemodynamic stability in the intraoperative period [2,3]. Clonidine and dexmedetomidine have also been shown to have significant analgesic affect in the post-operative period much after the regression of the motor blockade which allows for early and pain free ambulation [9,10].

In the view of these facts, this study was planned to compare the effects of dexmedetomidine and clonidine on duration of analgesia, motor and sensory blockade and the intraoperative hemodynamic profile when used as an adjuvant to bupivacaine. This study also aims to ascertain the safety of these drugs for use in routine hospital practice.

Materials and methods

Study design and subjects

This was a unicentric prospective randomized, single blinded, observational study done in Department of Anaesthesiology, Calcutta National Medical College in association with Urology, orthopaedic and gynaecology & obstetrics during February, 2012 to March, 2013. The patients (age: 18-65 years) undergoing elective infra-umbilical surgery in supine position having American Society of Anaesthesiology physical status I and II. The patients with

allergy to study drugs, contra-indication to spinal anaesthesia, obstetric patients, uncontrolled and labile hypertension, addiction to any substances like opium, alcohol, patients taking sedative drugs, suffering from uncontrolled diabetes, any kind of neurological illness, psychological illness, having spinal deformity, Hepatic or renal disorders or Haematological disorder were excluded from the study. Clearance from the institutional ethics committee is obtained first. Informed consent from patients were also obtained.

Sample size

Sample size was calculated from a similar study done by Kanazi et al., [3] in 2006, taking that as our reference study. Kanazi et al., in 2006 found the mean duration of 2 segment regression in dexmedetomidine group was 122 minutes (standard deviation 37 minutes) and in clonidine group 101 minutes (standard deviation 37 minutes). Using this data, the minimum number of patients required in each group is 25 [taking significant p value <0.05 (i.e. α error 5%), power of study 80% (i.e. β error 0.2) and software used is “computer programmes for epidemiologists (PEPI) by J. H. Abramson and Paul M. Gahlinger version 4.0x”]. For convenience 30 patients have been taken in each group. So, total sample size is $30+30 = 60$. Total sample size i.e. 60 patients were randomly divided into 2 groups of 30 patients each using a computer generated random number table. Groups were designated according to the study drug received, as follows: Group D- received 2.6 ml of hyperbaric bupivacaine (13 mg) and 5 μ g of dexmedetomidine (0.05 ml) and 0.35 ml of normal saline and Group C- received 2.6 ml of hyperbaric bupivacaine (13 mg), 37.5 μ g of clonidine (0.25ml) and 0.15 ml normal saline.

Procedure

The patients were again checked on the day before surgery and counselled again about the anaesthesia procedure. They were also advised to take a tablet ranitidine 150 mg before supper, light meal and tablet alprazolam 0.25 mg at bed time on the night before surgery and would remain nil by mouth after that. They were asked to take tab ranitidine 150 mg on the morning of surgery with sips of water and also to continue their usual medication, if any. On arrival to the operating theatre, the identity of the patient was confirmed and consent was checked. Then monitors are attached and baseline parameters were noted. ECG, SpO₂ and non-invasive blood pressure (NIBP) were monitored before, during and after the surgery. The subarachnoid block was performed with the study drugs with the patient in standard sitting position with a 25G Quinke’s needle at L3-L4 intervertebral space using midline approach maintaining strict aseptic condition. After spinal injection patients were positioned in supine position and oxygen was provided through a nasal cannula at 2 litres per min. After 2 minutes, every 2 minutes sensory nerve block was assessed bilaterally by using insensitivity to cold (when cotton swab soaked with alcohol was applied) in the midclavicular line. Motor blockade was assessed by using the modified Bromage scale [11] bilaterally every 2 minutes. The regression for sensory and motor block was checked every 15 minutes in a post anaesthesia care room. Patients were discharged from the post anaesthesia care room after sensory block regresses to S1 dermatome level and motor block to Bromage 0. No analgesic drug was given in the immediate post-operative period until the patient requested for analgesia and time for first analgesia will be recorded. Any incidence of adverse effects in the intraoperative or immediate postoperative period were noted and again patients were followed up at 24 hours in the ward for incidence of nausea, vomiting or any other adverse reaction.

Data collection

A pretested proforma was used to collect the patients details such demographic (Age, Sex, Body weight and Height, clinical parameters [Heart rate, Blood pressure - systolic, diastolic and mean arterial pressure, O₂ saturation (SpO₂), Time to achieve sensory block of T10, Time to achieve peak level of sensory block, Peak sensory block level, Time to achieve Bromage score 3 motor block, Time to regress 2 segments from peak level, Time taken to regress to S1 segment, Time of 1st analgesic request and Time to regain Bromage score 0] and adverse effects (Bradycardia, Hypotension, Arrhythmia, Sedation, Respiratory depression, Nausea and vomiting, and Post Dural puncture headache).

Data Analysis

Discrete categorical data are presented as Number and percentage; continuous data are given as mean \pm Standard deviation. Differences in demographic, anaesthetic and post-operative data were tested by independent Student's t-test (continuous data) or by Pearson Chi-square test and Fisher's exact test (categorical data). A p value less than 0.05 is taken as significant.

Results

A total of 60 patients (40% were male and 60% were female) were enrolled into study. In group-C 50% were male and 50% were female and in group-D 60% were male and 40% were female. In group-C 53.33% were Hindu and 46.67% were Muslim and in group-D 46.67% were Hindu and 53.33% were Muslim. When compared with students t test age and weight were comparable between both groups with all insignificant p values (Table 1).

Table 1: Baseline characteristics of the patients

Variables	GROUP-C	GROUP-D	p value
Age (years)	43.4 \pm 12.62	41.37 \pm 12.98	0.796
Weight (kgs.)	57.15 \pm 4.61	55.52 \pm 3.43	0.295
Height (cms.)	158.03 \pm 4.32	161.32 \pm 3.89	0.009
BMI (kg/m ²)	22.96 \pm 2.52	21.37 \pm 1.73	0.015
Gender			
Female	15	12	0.436
Male	15	18	
Religion			
Hindu	16	14	0.605
Muslim	14	16	

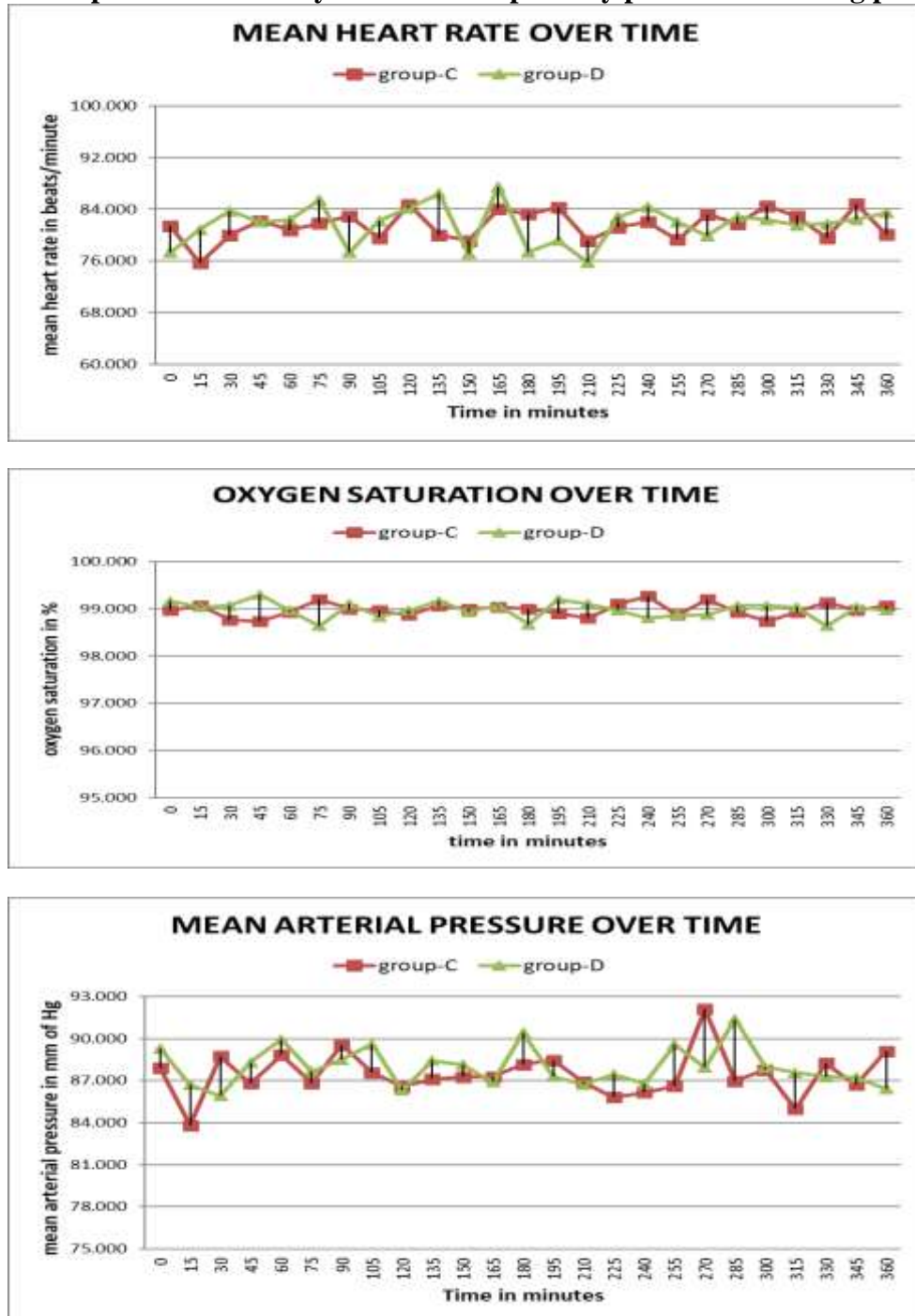
In our study, maximum surgery performed were lower limb orthopaedic surgery (35%), then TURP (23.33%), then vaginal hysterectomy (21.66%) and total abdominal hysterectomy (20%). Type of surgery in different groups were almost identical. Number of ASA physical status I and ASA physical status II patients were comparable in both groups (Table 2).

Table 2: Surgical characteristics of the patients

Variables	GROUP-C	GROUP-D	p value
Type of surgery			
Total Abdominal Hysterectomy	7	5	0.771
TURP	8	6	
Lower Limb Orthopaedic Surgery	9	12	
Vaginal Hysterectomy	6	7	
ASA physical status			
ASA physical status I	25	23	0.518
ASA physical status II	5	7	

In our study, there was no fall or excess rise of heart rate in any group at any specific time period and mean heart rate in both groups were comparable over time. As oxygen saturation of different groups were almost identical with each other, it can be concluded that there was no hemodynamic and respiratory problem in any group. There was no fall or rise of mean arterial pressure in any group intraoperatively or postoperatively and the mean arterial pressure of both groups were comparable ($p>0.05$) so, it can be said that both clonidine and dexmedetomidine preserve hemodynamic stability when used as intrathecal adjuvant to hyperbaric bupivacaine (Figure 1).

Figure 1: Comparison of hemodynamic and respiratory parameters among patients



In our study the mean time to achieve T10 level sensory block in group-C was 5.93 ± 1.33 minutes and in group-D was 6 ± 1.49 minutes. In group-C patients time for 2 segment regression was 125.5 ± 13.35 minutes and in group-D patients higher (157 ± 11.64 minutes). So, it can be said that both clonidine and dexmedetomidine prolongs the 2-segment regression time but dexmedetomidine is superior in prolonging 2 segment regression time. In group-C patients S1 regression time was 247.5 ± 23.22 minutes and in group-D patients higher (303 ± 25.66 minutes). So, it can be said that both clonidine and dexmedetomidine prolongs the time for regression to S1 level but dexmedetomidine is better alternative in prolonging the time for regression to S1 level. Group-C patients took 217.5 ± 23.55 minutes to regain Bromage score 0 and group-D patients took 260.5 ± 20.27 minutes. So, motor blockade was also prolonged in dexmedetomidine group than in clonidine group. Group-C patients asked after 186.5 ± 17.03 minutes but group-D patients requested for analgesic much later i.e. after 249 ± 22.83 minutes. So, the inference would be that both dexmedetomidine and clonidine increases the time of post-operative analgesia but dexmedetomidine do more so (Table 3).

Table 3: Comparison of sensory and motor block anaesthetic features among patients

Variables	GROUP-C	GROUP-D	p value
T10 sensory block time (minutes)	5.93 ± 1.33	6 ± 1.49	0.982
Peak level of sensory block			
T4	7	5	0.772
T5	13	13	
T6	10	12	
Peak sensory block time (minutes)	12.27 ± 1.80	13.53 ± 1.72	0.030
BROMAGE 3 motor block time (minutes)	7.67 ± 1.97	7.13 ± 1.63	0.566
2 segment regression from peak level (minutes)	125.5 ± 13.35	157 ± 11.64	<0.0001
Time to regress to S1 segment (minutes)	247.5 ± 23.22	303 ± 25.66	<0.0001
Time to regress to BROMAGE 0 motor block (minutes)	217.5 ± 23.55	260.5 ± 20.27	<0.0001
Time to 1st analgesic request (minutes)	186.5 ± 17.03	249 ± 22.83	<0.0001

The incidences of different side effects were low in the perioperative period upto a period of 24 hours and they were comparable between both the groups ($p > 0.05$) (Table 4).

Table 4: Side effects of the anaesthesia among patients

Side effects	GROUP-C	GROUP-D	p value
Bradycardia	3	2	0.64
Hypotension	2	3	0.64
Nausea & Vomiting	3	2	0.64
Post Dural Puncture Headache	2	1	0.553

Discussion

The mechanisms of the analgesic action of α_2 -agonists have not been fully elucidated. The activation of inwardly rectifying G1-protein-gated potassium channels results in membrane hyperpolarization decreasing the firing rate of excitable cells in the central nervous system (CNS). This is considered a significant mechanism of inhibitory neuronal action of α_2 -adrenoceptor agonists [12]. Another prominent physiologic action ascribed to α_2 -adrenoceptors is their reduction of calcium conductance into the cell, thus inhibiting neurotransmitter release [12].

These two mechanisms represent two very different ways of effecting analgesia: in the first, the nerve is prevented from ever firing, and in the second, it cannot propagate its signal to its neighbour. Activation of the receptors in the brain and spinal cord [13] inhibits neuronal

firing causing hypotension, bradycardia, sedation, and analgesia. In general, presynaptic activation of the α_2 -adrenoceptor [13] inhibits the release of norepinephrine terminating the propagation of pain signals.

Postsynaptic activation of α_2 -adrenoceptors in the central nervous system inhibits sympathetic activity and thus can decrease blood pressure and heart rate.

Administration of an α_2 -agonist via an intrathecal or epidural route provides an analgesic effect in postoperative pain without severe sedation [14]. This effect is due to the sparing of supraspinal CNS sites from excessive drug exposure, resulting in robust analgesia without heavy sedation.

In our study we compared the duration of sensory and motor block in the two groups of patients, Group C was given intrathecal bupivacaine plus clonidine & group D was given intrathecal bupivacaine plus dexmedetomidine. We found that the Group C patients had prolonged motor and sensory blockade ($p < 0.05$). These results were similar to the findings reported by Seah et al., [15] and Racle et al., [16] in their studies done on patients who underwent TURP and orthopaedic surgeries respectively.

In either of the groups, we did not observe any increased hypotension either during or after anaesthesia. Further there was no statistically significant bradycardia. But this is in contrary to what has been observed by Seah et al., [15] and Racle et al., [16]. In the studies done by Seah et al., [15] and Racle et al., [16], higher incidence of side effects such as hypotension and bradycardia were reported in the clonidine group and such patients were treated with IV Ephedrine and IV Atropine respectively. This higher incidence of side effects may be attributed to the higher dose (150 μg) of clonidine received by the patients in these studies as compared to a lower amount (37.5 μg) received by patients in our study. Chiari et al., [17] have substantiated the fact that higher incidence of side effects such as hypotension and bradycardia increases with the increase in the dose of clonidine ($>100 \mu\text{g}$).

Singh et al., [18] in 2012 compared intrathecal clonidine and dexmedetomidine with intrathecal hyperbaric bupivacaine and concluded that though both clonidine and dexmedetomidine prolonged duration of sensory and motor block of bupivacaine, dexmedetomidine is better in terms of longer duration of action. They did not find any increase in side effects.

Thus, dexmedetomidine a newer α_2 agonist seems to be an attractive adjuvant to spinal bupivacaine even in doses as low as 5 μg . Clonidine can be considered a good choice as adjuvant, if its dose is kept at a lower level range ($<100 \mu\text{g}$). However, dexmedetomidine provides longer duration of sensory and motor block and post-operative analgesia when compared with clonidine. The incidence of side effects is low with both drugs if their doses are kept in lower range.

The hemodynamic effects of clonidine and dexmedetomidine are due, in part, to actions in the brain and the periphery [19]. Clonidine and dexmedetomidine affect blood pressure in a complex fashion after neuraxial or systemic administration because of opposing actions at multiple sites [20,21]. In addition to brainstem and peripheral sites of actions, intrathecally administered clonidine directly inhibits sympathetic preganglionic neurons in the spinal cord [13]. As a result, the degree of clonidine induced hypotension is related to the spinal level of injection. At low thoracic or lumbar levels of injection, intrathecal clonidine is not associated with an increased incidence of hemodynamic side effects when compared with intravenous injection. Alternatively, direct inhibition of sympathetic preganglionic neurons in the upper thoracic dermatomes, which supply the heart, may also have a more profound impact on resting blood pressure than does the inhibition of sympathetic preganglionic neurons elsewhere [13]. Both of these combinations i.e. clonidine or dexmedetomidine with bupivacaine provide prolonged sensory and motor blockade, haemodynamic stability, minimal side effects and excellent intraoperative and postoperative analgesia.

Conclusion

Our conclusion from the study is that clonidine and dexmedetomidine as intrathecal adjuvant significantly prolongs the sensory and motor blockade of intrathecal hyperbaric bupivacaine without altering the onset of spinal anaesthesia. In equipotent doses dexmedetomidine is more effective as intrathecal adjuvant to hyperbaric bupivacaine than clonidine. Neither clonidine nor dexmedetomidine increases side-effects of spinally administered hyperbaric bupivacaine if given in appropriate doses.

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