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Comparative Evaluation of Intraoperative IV Clonidine and Dexmedetomidine infusion in patients undergoing Spine Surgery under General Anaesthesia - A Randomized Double Blinded Study

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Abstract

Introduction: Alpha two agonists such as clonidine and dexmedetomidine have been popular in anaesthesia practice as adjuvants to provide sedation, anxiolysis, analgesia and controlled hypotension. Dexmedetomidine is eight times more selective for alpha 2 receptors than clonidine. **Aim**: The present study was undertaken to compare effects of clonidine and dexmedetomidine on haemodynamic stability, anaesthetics requirement and recovery profile in spine surgeries under general anaesthesia. **Material and Method:** A total 100 patients of American Society of Anaesthesiologists (ASA)grade I and II, age between 18 to 60 years, who were schedule for thoracic and lumbar spine surgery under general anaesthesia were included in the study. They were randomized in two groups of 50 patients in each. Group A received injection clonidine 2ug/kg bolus IV over 10 min followed by normal saline infusion and group B received injection dexmedetomidine 1ug/kg bolus IV over 10 minutes followed by dexmedetomidine infusion of 0.5ug/kg/hr. Assessment of haemodynamic parameters, anaesthetic requirement and recovery profile was done. **Results:** With clonidine and dexmedetomidine the intraoperative haemodynamic parameters remained stable without any statistical difference. Both the drugs were equally effective in reducing anaesthetic agent's requirement and in reducing blood loss while comparable with respect to recovery profile and adverse effects. Group B had lesser extubation time (9.72±4.1 minutes) than group A (11.44±4 minutes) which was statistically significant however it was not clinically significant ,whereas the time to achieve aldrete score of > 9 was comparable between two groups. **Conclusion:** Dexmedetomidine and clonidine have similar effects on haemodynamic stability, anaesthetics requirement and recovery profile.

Keywords: Clonidine, Dexmedetomidine, spine surgery, anaesthetic requirement, recovery

Introduction

Spine surgeries present special challenges to anaesthesiologists due to its specific needs of stable haemodynamics, relatively dry operative field, rapid recovery for early neurological assessment as well as careful perioperative positioning. These factors warrant the use of medications to maintain adequate depth of anaesthesia as well as specific needs of the surgery. The use of perioperative clonidine, dexmedetomidine, beta blocker (esmolol), opioids and magnesium sulfate have been reported to provide beneficial effects during general anaesthesia, however with varying success rate [1].

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Perioperative use of alpha-2 adrenoceptor agonists' decreases sympathetic tone, attenuates the stress responses to anaesthesia and surgery, provides sedation and postoperative analgesia. Clonidine and dexmedetomidine are alpha-2 adrenergic receptor agonists. Both the drugs act on alpha 2 receptors, however dexmedetomidine is eight time more selective than clonidine for alpha two receptors [2]. It acts on α2 receptors located at locus ceruleus in the brain stem. It has sedative and hypnotic action but maintains an arousable state. It produces dose-dependent sedation, anxiolysis, and analgesia without causing respiratory depression. It also has a shorter duration of action compared with clonidine. Few studies [3-9] in the literature demonstrate the effectiveness of clonidine and dexmedetomidine for providing intraoperative haemodynamic stability, decrease anaesthetic requirements and improved postoperative recovery in general anaesthesia.

Hence the present study was carried out with a prime objective to compare haemodynamic stability, anaesthetics requirement and recovery profile while secondary objective to compare average blood loss, duration of surgery and adverse effects between IV clonidine and IV dexmedetomidine in patients undergoing spine surgeries under general anaesthesia.

Materials and Methods

After obtaining Institutional ethics committee approval and written informed consent from the patients, this randomized, double blinded prospective study was conducted in 100 patients(50 patients in each group) of American Society of Anaesthesiologists (ASA) grade I and II, age between 18 to 60 years and who were undergoing thoracic and lumbar spine surgery under general anaesthesia between 0ctober 2014 to October 2015. Exclusion criteria included patients' refusal, patients with cardiac conduction defects, severe pulmonary, cardiac, hepatic or renal disease, patients on beta blockers, pregnant females, cervical spine surgery and heart Rate< 50 beats per minute.

Randomization was done by using Chit method.100 chits with 50 chits writing "C" for clonidine and 50 chits writing "D" for dexmedetomidine were prepared. After folding the chits, they were put in a box and mixed well. Eligible patients were allotted to one of the group by picking up chit and handing it to the person preparing the study drug. Both the study drug boluses and infusions were prepared by person not involved in the study and were given using syringe pump. The patients as well as the anaesthesiologists monitoring the patients were blinded about the study drug. For group A, iv clonidine 2 ug/kg was diluted with normal saline to make 10 ml bolus(in 10 ml syringe) and 0.9 % normal saline (in 50 ml syringe) for intra operative infusion was prepared. For group B, iv dexmedetomidine 1 ug/kg was diluted with normal saline to make 10 ml bolus(in 10 ml syringe) and 5ug/ml of dexmedetomidine (2.5 ml [250 ug]of dexmeditomidine was diluted with 47.5 ml of 0.9% normal saline)in 50 ml syringe for intra operative infusion was prepared. In this way both the drugs were made to look similar to avoid bias.

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A pre-anaesthetic evaluation including history, thorough physical examination and complete neurological assessment along with airway examination was done. Baseline investigations like Haemoglobin, Complete blood count, Liver function tests along with prothrombin time and INR (International normalized Ratio), Renal function Tests, Serum electrolytes, x-ray chest, and Electrocardiogram(ECG) were performed. Those patients who met the eligibility criteria were approached for participation in the study and written informed consent was obtained. On day of surgery after confirming adequate starvation patients were randomized into either of two groups. Patients were taken in the operation theatre and intra-venous access of 18 G was secured and multipara monitors such as ECG, Pulse-oximeter(spo2), non- invasive blood pressure(NIBP) and after intubation carbon dioxide monitor(Et Co2) were attached and baseline parameters were noted. Thereafter study drug as bolus was given over 10 minutes using syringe pump. Group A received clonidine bolus of 2ug/kg IV over 10 min and group B received dexmedetomidine bolus of 1ug/kg IV over 10 minutes. Heart Rate (HR),Blood Pressure(BP) and SpO2 were noted at the start and end of bolus infusion. Following this all patients were pre-medicated with injection midazolam 0.03mg/kg and fentanyl 2ug/kg. Anaesthesia was induced with injection propofol 1-2mg/kg, till the loss of verbal contact and neuromuscular blockade was achieved with atracurium 0.5mg/kg. After 3 minutes of mask ventilation, the patient's trachea was intubated with appropriate size cuffed endotracheal tube. Anaesthesia was maintained with nitrous oxide in oxygen 50:50 and isoflurane (MAC value of 0.8 to 1). Muscle paralysis was maintained with atracurium infusion @ 5ug/kg/min. HR, BP, EtCo2 and SpO2 were noted at time of intubation, then 1, 3 and 5 minutes after intubation. The patients were turned to prone position on the standard operation table and pressure points were padded with cotton rolls. Study drug infusion was started as soon as the patient was turned prone and was continued till the end of skin closure. Volume of study drug infusion to be given was calculated as follows: weight of patient/10=n(ml/hr). Patients in clonidine group received infusion of 0.9% normal saline and those in dexmedetomidine group received infusion of dexmedetomidine 0.5ug/kg/hr.

After making the patient prone HR, BP, SPo2 and EtCo2 were noted at 1, 5, 15 minutes and then every 15 minutes till the end of skin closure. Intravenous diclofenac (1mg/kg) or paracetamol (1g) was given for analgesia at the beginning of skin closure. BP was targeted to keep within 20% of the baseline value. Hypotension (more than 20% drops from the baseline value) was treated with a bolus dose of 5mg ephedrine or 50 to 100µg phenylephrine bolus according to the HR. Hypertension (more than 20% rise from the baseline value) was treated with a bolus dose of fentanyl (1ug/kg). If the BP was not controlled with 2 boluses of fentanyl, then propofol bolus (0.5 mg/kg) was given. If BP was still not controlled even with 2 bolus dose of propofol, then beta blockers such as esmolol and labetalol were used. The number of episodes of bradycardia (HR<50/min) was noted. End Tidal isoflurane concentration (ET Iso) was decreased by 50% at the start of skin closure and turned off at the end of skin closure. Anti-emetic in form of ondansetron (0.1mg/kg) was given at the time of closure.

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After completion of surgery, residual neuromuscular block was reversed with neostigmine (0.05mg/kg) and glycopyrrolate (8ug/kg). The patient's trachea was extubated after meeting the extubation criteria and the time of extubation was noted. Recovery scores were noted based on Aldrete criteria score. Then both the groups were compared with respect to intraoperative haemodynamic parameters, anaesthetic requirement, recovery profile, average blood loss, duration of surgery and adverse effects.

Statistical analysis

When applicable, data was statistically described in terms of mean (±SD), frequencies (number of cases) and percentages. First data was tested for normal distribution by Klomogorov– Smirnov test. Then if normally distributed comparison of quantitative variables between the study groups was done using Student t test for independent samples and for non-normally distributed quantitative and ordinal data Mann–Whitney U test was used. Chi square test was performed for comparing categorical data and Fisher Exact test was used instead when the expected frequency is less than 5. A probability value (p value) of < 0.05 was considered statistically significant in our study. Also computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc. Chicago, IL, USA) version 17 was used for doing all statistical calculations. Sample Size Estimation: Sample size was calculated by nmaster 1.0. A type I error of 0.05 and a type II error of 0.80 was accepted for detecting a true difference. As a result, we calculated that minimum 50 patients are needed in each group in order to obtain 5% type 1 error and an 80% power of detecting a difference of 0.5 or more. All observations were recorded on a proforma.

Observations and Results

The present study was carried out in 100 patients, among them 56 (56.0%) were males and 44 (44.0%) were females. The demographic data with respect to age, sex, weight and ASA status of the patients in both the groups were comparable and no statistically significant difference was found. (Table 1).

Table 1: Demographic data of the patients

Parameters	Group A	Group B	P value
Age (Years)	39.08±12.48	39.82±11.22	0.76
Sex (M/F)	33(66%)/17(34%)	23(46%)/27(54%)	0.07
Weight (Kg)	56.78±10.54	56.42±8.70	0.85
ASA Grade I/II	34(68%)/16(32%)	38(76%)/12(24%)	0.54

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With injection clonidine and dexmedetomidine the intraoperative haemodynamic parameters like heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressures (MBP), remained stable without any statistical difference (Figure 1).

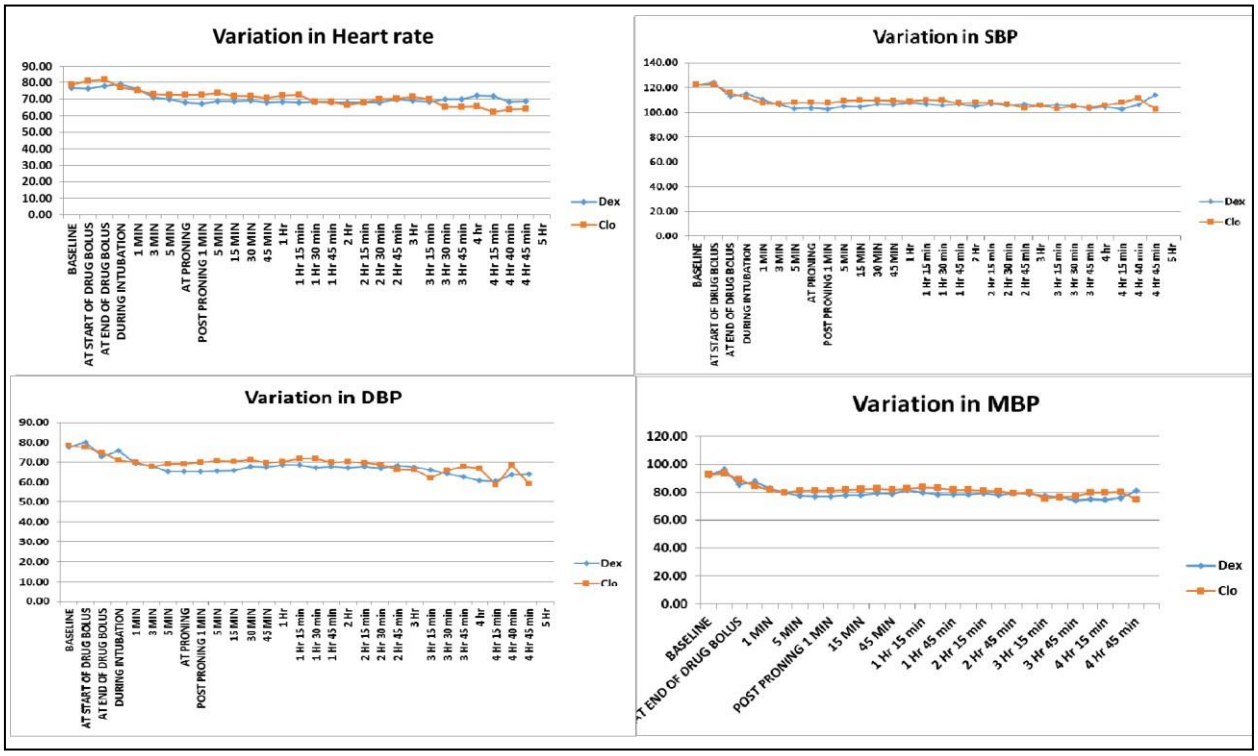

Figure 1:Comparison of haemodynamic parameters between two groups

Requirement of fentanyl and propofol were comparable between two groups and no statistically significant difference was observed with the P value of 0.167 and 0.092 respectively(Table 2). Dexmedetomidine group (Group B) had lesser extubation time (9.72±4.1 minutes) than clonidine group (group A) (11.44±4 minutes) which was statistically significant, whereas the time to achieve aldrete score of > 9 was comparable between the two groups (Table 2). The average blood loss and duration of surgery were comparable between two groups with no statistically significant difference (Table 2).

Table 2: Shows the anaesthetic requirement, recovery profile, average blood loss and duration of surgery

Variable		**Group A**	**Group B**	**P Val**
Anaesthetic requirement	Total dose of fentanyl used	127.20±35.83	118.60±24.95	0.167
	Total dose of propofol used	141.00±31.38	130.60±29.72	0.092
Recovery Profile (Min.)	Extubation time	11.44±4	9.72±4.1	0.036
	Time to achieve aldrete score of >9	3.98±1.45	3.78±1.33	0.474
Average blood loss (ml)		296.96+115.19	342.40+133.32	0.071
Duration of surgery (Min.)		169.50+ 62.53	183.47+ 60.25	0.11

In clonidine group ,4 patients had hypotensive episodes where as in dexmedetomidine group, 3 patients had hypotensive episodes which were not statistically significant (p value-1.0). Similarly in clonidine group, 7 patients had episodes of bradycardia whereas in dexmedetomidine group, 4 patients had episodes of bradycardia which were not statistically significant (p value-0.52). The number of episodes of hypertension/ tachycardia was comparable between the clonidine and dexmedetomidine group and no statistically significant difference were observed (p value-0.78).

Discussion

Perioperative hemodynamic stability is one of the most important concepts during spine surgery. During surgery, low arterial pressure predisposes patient to spinal cord ischemia, On the other hand abrupt rise in arterial pressure may cause bleeding in the operating field. In addition to haemodynamic stability, rapid and smooth recovery from anaesthesia is also important for immediate neurological assessment in patients undergoing spine surgery. Various anaesthetic techniques have been tried in this regard to maintain stable hemodynamic environment and to gain rapid recovery following these surgeries. Alpha 2 agonists are known to provide sedation, anxiolysis, analgesia and controlled hypotension. In this randomized clinical trial we have compared the two alpha 2 agonists: clonidine and dexmedetomidine with respect to their effects on haemodynamic stability, anaesthetics requirement and recovery in patients undergoing spine surgery under general anaesthesia.

The current study demonstrated that perioperative use of clonidine and dexmedetomidine have comparable effect on haemodynamic stability as well as reduced anaesthetic consumption. The demographic data (age, sex, weight, ASA status) and duration of surgery in both the randomized groups were comparable and there was no statistically significant difference between two groups and that above parameters had no influence on outcome of the study.

There were no statistically significant differences between the two groups in terms of heart rate, systolic, diastolic and mean arterial blood pressure. The intergroup comparison showed p value >0.05 at all time. This implied that both clonidine and dexmedetomidine have comparable effects on haemodynamic parameters. **Chandrasekaraiah MM et al**[7] studied the effects of clonidine premedication on haemodynamic changes during Laparoscopic cholecystectomy .They observed that there was significant reduction of heart rate (16.6003), systolic pressure (22.433) and mean arterial pressure (14.8) p value<0.001. Hence they concluded that clonidine premedication can effectively counteract the cardiovascular changes induced by pneumoperitoneum. **S Kumar et al**[11] did a study comparing the effects Of Dexmedetomidine and Clonidine premedication on perioperative haemodynamic stability and postoperative analgesia in Laparoscopic Cholecystectomy. In their study sixty patients were divided into two groups where Group 1

received 2 µg/kg of clonidine diluted in normal saline, given slow intravenous infusion over 10 min and Group 2 received 1 µg/kg of dexmedetomidine diluted in normal saline, given slow intravenous infusion over 10 min before induction of GA. They found that dexmedetomidine and clonidine are effective in attenuating the hemodynamic response to pneumoperitoneum with equal efficacy. **Anand Subramaniam et al[12]** performed a study evaluating efficacy of intravenous clonidine vs intravenous dexmedetomidine in attenuating the hemodynamic response to laryngoscopy and intubation. In their study patients were divided into two groups, group C n=30 received clonidine 1µgm/kg intravenously infusion before intubation and group D n=30 received dexmedetomidine 1µgm/kg intravenously 10 minutes as infusion before intubation. The haemodynamic variables were noted at 1, 3 and 5 minutes after intubation. They did not find any statistically significant difference between the two groups with respect to the heart rate, systolic and diastolic blood pressure, mean arterial pressure or the rate pressure product. Hence they concluded that clonidine and dexmedetomidine are equally effective in reducing the stress response to Laryngoscopy and intubation. Our findings were correlated with previous studies.

We analyzed the requirement of anaesthetics as the amount of fentanyl and propofol required to maintain hemodynamics between two groups. We kept Isoflurane concentration of MAC 0.8 to 1.0 for all patients. Requirement of fentanyl and propofol were comparable between the clonidine and dexmedetomidine groups and no statistically significant difference was observed with the P value of 0.167 and 0.092 respectively. **Keniya VM et al[8]** studied efficacy of dexmedetomidine in attenuating sympathoadrenal response to tracheal intubation and analysed reduction in intraoperative anaesthetic requirement. They found that requirement of thiopentone and isoflurane was decreased by 30% and 32%, respectively, in the dexmedetomidine group as compared to the control group. Also the requirement of fentanyl during the operation was 100±10 µg in the control group whereas it was 60±10 µg in the dexmedetomidine group. Hence they concluded that perioperative infusion of dexmedetomidine is effective in attenuating sympathoadrenal response to tracheal intubation and has significant anaesthetic and opioid sparing effect. **Mariappan R et al[2]** compared the effects of oral clonidine premedication with intraoperative dexmedetomidine infusion on anaesthetic requirement and recovery from anaesthesia in patients undergoing major spine surgery. In this study 74 patients were randomly allocated to receive either oral clonidine premedication or intraoperative dexmedetomidine infusion. They found that both the drugs have anaesthesia sparing effect; however it was more with dexmedetomidine. Our study was in accordance with other studies .[(3-5, 13).]

The postoperative recovery was assessed in the form of extubation time and aldrete criteria scores between the two groups. Extubation time was taken as the time from stopping Isoflurane to extubation whereas Recovery time was taken as the time to achieve Aldrete score >9. The mean extubation time in both the groups were compared. The mean extubation time in clonidine group was 11.44$\pm$4 minutes and in dexmedetomidine group it was 9.72 $\pm$ 4.1 minutes and the difference was statistically significant (p value= 0.036). So the Dexmedetomidine has significant lesser extubation time than clonidine. The time to achieve Aldrete criteria scores of >9 was compared between both the groups. In clonidine group it was 3.98$\pm$1.45 minutes whereas

in dexmedetomidine group it was 3.78±1.33 minutes with P value of 0.474 which was not statistically significant. **Mariappan R et al**[2] compared the effects of oral clonidine premedication with intraoperative dexmedetomidine infusion on anaesthetic requirement and recovery from anaesthesia in patients undergoing major spine surgery. Recovery from isoflurane anaesthesia was similar with both clonidine and dexmedetomidine groups.

We observed less bleeding in the clonidine group (296.96+115.19) than in the dexmedetomidine group (342.40+133.32) with P value of 0.071 which was not statistically significant and result was similar to previous studies.[13-15]

Hypotension and bradycardia are well known adverse effects of alpha 2 agonists. In our study episodes of hypotension and bradycardia as well as episodes of hypertension/ tachycardia were comparable between the clonidine and dexmedetomidine group with no statistically significant difference. These observations were correlated with other studies.[13,16]

The limitations of our surgery were lack of placebo group to compare the haemodynamic stability, anesthetics requirement and recovery and non availability of Bispectral index monitoring.

Conclusion

In present study, both the study drugs (clonidine and dexmedetomidine) have similar effects on intraoperative haemodynamic stability, are equally effective in reducing anaesthetic agent's requirement and were comparable with respect to recovery profile. Also both the drugs were equally effective in reducing blood loss and have comparable adverse effects.

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