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DEXMEDETOMIDINE PROVIDES BETTER HEMODYNAMIC STABILITY COMPARED TO CLONIDINE IN SPINE SURGERY

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ABSTRACT

Introduction: Spine surgery presents a number of challenges to the anesthesiologist. The α_2 adrenergic agonist drugs are commonly used in such cases to provide hemodynamic and sympathoadrenal stability. Dexmedetomidine (DEX) is one of the most potent and highly selective α_2-adrenergic receptor agonists. Another α_2 adrenergic agonist drug that is used widely is clonidine. The study aims to compare both drugs in terms of hemodynamic stability in spine surgeries.

Patients and Methods: 30 patients underwent spinal surgery were classified into one of the following group: DEX group (received DEX 1 mcg/kg in 10 minutes followed by 0.5 mcg/kg/hour during the course of the surgery) or CLO group (received clonidine 1 mcg/kg in 10 minutes followed by 1 mcg/kg/hour during surgery), by consecutive sampling. All other treatments and medications were similar in both groups. The systolic and diastolic blood pressure, mean arterial pressure, and heart rate were recorded every 5 minutes. Data was then analyzed by SPSS.

Result: The patients in the DEX group had a better mean arterial pressure (p=0.002) and heart rate (p=0.018) stability compared to those in the CLO group.

Conclusion: The administration of dexmedetomidine provides a better hemodynamic stability compared to clonidine in patients underwent spinal surgery.

Keywords: Spine surgery, Dexmedetomidine, Clonidine, Hemodynamic Stability.
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INTRODUCTION

Spine surgery presents some challenges to the anesthesiologist. Patients underwent spinal surgery such as microdiscectomy, reconstructive surgery, decompression surgery, vertebral fracture fixation, or debridement fixation may result in significant intraoperative blood loss and postoperative acute pain.[1]

The significance of reducing the bleeding on spinal surgery is not only important for maintaining the patient's hemodynamic stability but also enables a better surgical field, with all its fragile, major neurological structures. Maintaining a clear surgical field helps the surgeon to reduce surgery time, which in turn reduces the total blood loss, thus maintaining a better hemodynamic stability.

Hemodynamic stability in spinal surgery is desirable to perform rapid recovery for early neurologic assessment and management of complications. It is therefore mandatory for anesthesiologists to choose techniques that allow hemodynamic stability during the procedure.[2] The alpha-2 agonist group is a new class of drugs with different mechanisms of action from other commonly used anesthetic agents. Dexmedetomidine (DEX) is one of the most potent and highly selective α2-adrenergic receptor agonists, with an affinity for α2:α1 receptor bindings in the ratio of 1,620:1. DEX possesses a hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without producing significant respiratory depression.[3] Its central and peripheral sympatholytic actions are mediated by binding to the alpha-2 adrenergic receptors resulting in decreased mean arterial pressure (MAP), heart rate (HR), cardiac output, and norepinephrine release.[2]

Another alpha-2 adrenergic agonist group is clonidine. Clonidine has sedative, analgesic, and anti-anxiety effects decreases the need for anesthetic drugs and maintaining perioperative hemodynamic stability and sympathoadrenal stability.[4-6]

Despite some clinical trials that study the effectiveness of DEX and clonidine in reducing intraoperative bleeding in adults, only little is known about their effects in maintaining intraoperative hemodynamics in spinal surgery.[2] It is well-known that spinal surgery has many complications such as postoperative hematoma development, recurrent laryngeal nerve paralysis (RLN), and vascular damage.[7,8] The goal of this study was to compare the effect of DEX and clonidine as adjuvants in anesthesia in providing hemodynamic stability in patients undergoing spinal surgery.

PATIENTS AND METHODS

This is an observational cohort study. 30 patients were enrolled in this study by consecutive sampling.

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This study was approved by the Committee of Ethical Research of Udayana University/Sanglah Hospital. All subjects provided a written consent to be included in this study.

Inclusion criteria include those aged 18-65 years old, body mass index (BMI) 18.5-23.0 kg/m^2, physical status ASA I-II, who underwent spinal surgery. And the exclusion criteria were those whose history of allergy to anesthetic drugs, those whose history of allergy to alpha-2 agonist drugs, those with a history or presenting heart and/or vascular disease, pregnancy, those with a history of hypertension, and eventful surgery (i.e. massive bleeding).

Patients who met eligibility criteria were randomly divided into 2 groups, the dexmedetomidine group (DEX group) and the clonidine group (CLO group). The patients in the DEX group were given dexmedetomidine 1 mcg/kg in 10 minutes, followed by maintenance dose at 0.5 mcg/kg/hour during the course of the surgery, until the skin closure was completed. Those in the CLO group were given clonidine 1mcg/kg in 10 minutes, followed by maintenance dose at 1 mcg/kg/hour during the course of the surgery, until the skin closure was completed. The hemodynamic status data were recorded every five minutes. They include the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR).

Otherwise, all medications used for all patients in both groups were the same. Those include ringer lactate infusion 3 ml/kg in 20 minutes, midazolam 0.05 mg/kg, fentanyl 2 mcg/kg, propofol 2.5 mg/kg, and atracurium 0.5 mg/kg. We use standard ASA monitoring devices like sphygmomanometer, peripheral oxygen saturation, bispectral index, ECG, end-tidal CO2 (EtCO2), and oral temperature. All patients involved were mechanically ventilated (tidal volume of 6-8 ml/kg, respiration rate at 12-16 with targeted EtCO2 30-35 mmHg), and anesthesia was maintained using compressed air at 2 liters per minute (LPM), oxygen 2 LPM, and sevoflurane 1.5-2.5% (using targeted BIS at 40-55).

We used SPSS 22.0 for data analysis. Shapiro-Wilk, Mann-Whitney, independent t, Levene, and chi-square tests were used in the analysis, where a p-value of <0.05 was considered statistically significant.

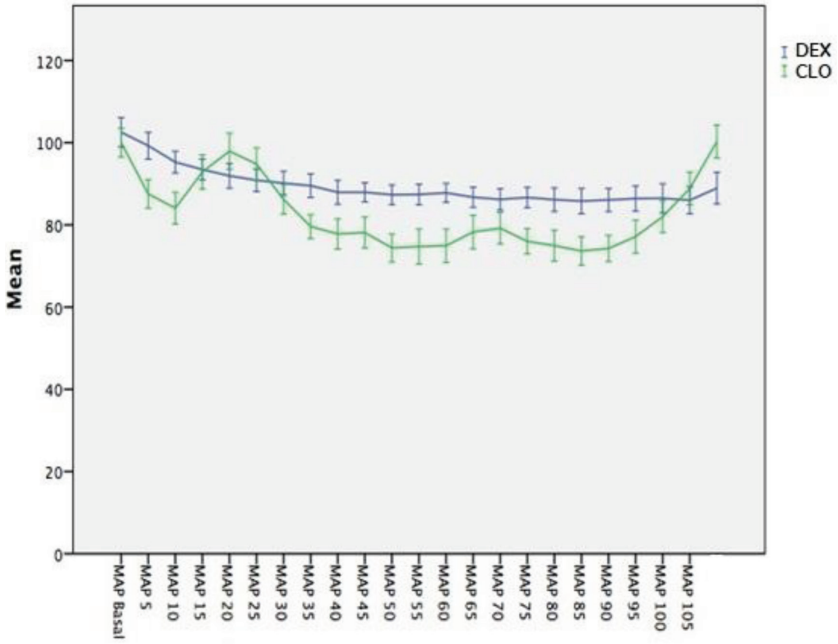

Figure 1 MAP comparison trend

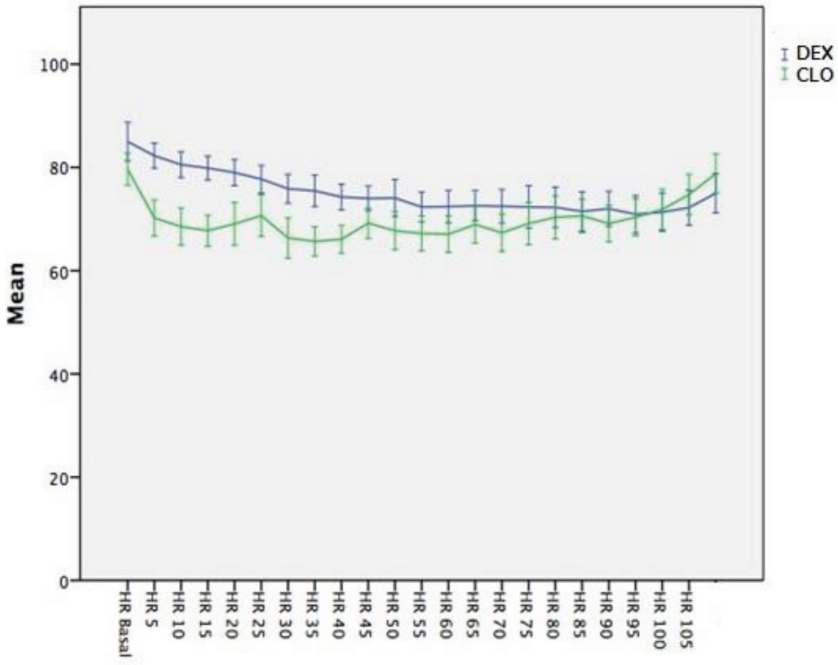

Figure 2 HR comparison trend

RESULTS

30 patients were enrolled for this study, with a group consisted of 15 subjects. The median age for the DEX group was 46, compared to 55 in the CLO group. The subjects' characteristics are shown in Table 1.

Significant differences in the MAP were found in the 10th minute, which was the time where the full dose of the loading dose of dexmedetomidine or clonidine was administered (95.3 ± 4.8 vs. 84.1 ± 6.9, p <0.001). The difference between MAP and HR in both groups were shown in Table 2 and Table 3, respectively. Figures 1 and 2 displayed a pattern where it is visible that dexmedetomidine provides a better MAP and HR stability compared to clonidine.

Table 1 Subjects' characteristic

Variables	Groups	
	DEX (N=15)	CLO (N=15)
Age, years (median(IQR)	46 (32)	55 (21)
Gender		
Male, n(%)	10 (66.7)	13 (86.7%)
Female, n(%)	5 (33.3)	2 (13.3%)
BMI, kg/m^2 (mean±SD)	22.4±2.9	23.3±3.3
ASA		
I	1 (6.7)	1 (6.7)
II	14 (93.3)	14 (93.3)
Surgery duration, minutes (median, IQR)	175 (70)	145 (75)

Table 2 MAP comparison of both groups

MAP	Group		p-value	Mean difference	CI (95%)
	DEX (n=15)	CLO (n=15)			
Baseline	102.5 ± 6.4	100.0 ± 6.3	0.283	2.533	-2.209 - 7.276
5	99.3 ± 5.9	87.5 ± 6.3	0.000	11.733	7.173 - 16.293
10[a]	95.3 ± 4.8	84.1 ± 6.9	0.000	11.200	6.739 - 15.661
15[b]	93.5 ± 4.6	92.9 ± 7.5	0.793	0.600	-4.044 - 5.244
20	91.9 ± 5.4	97.9 ± 7.9	0.022	-6.000	-11.077 - -0.923
25	90.8 ± 4.9	94.8 ± 7.1	0.087	-3.933	-8.483 - 0.617
30[c]	90.1 ± 5.2	86.2 ± 6.4	0.076	3.933	-0.442 - 8.309
35	89.5 ± 5.2	79.6 ± 5.2	0.000	9.933	6.054 - 13.813
40	87.9 ± 5.2	77.8 ± 6.6	0.000	10.133	5.669 - 14.597
45	87.9 ± 4.2	78.1 ± 6.8	0.000	9.800	5.586 - 14.014
50	87.3 ± 4.3	74.4 ± 6.1	0.000	12.933	8.973 - 16.894
55	87.4 ± 4.5	74.7 ± 7.7	0.000	12.667	7.943 - 17.390
60	87.8 ± 4.1	74.9 ± 7.3	0.000	12.867	8.421 - 17.313
65	86.7 ± 4.4	78.3 ± 7.3	0.001	8.467	3.939 - 12.994
70	86.2 ± 4.7	79.2 ± 6.9	0.003	7.000	2.587 - 11.413
75	86.7 ± 4.4	76.0 ± 5.5	0.000	10.667	6.923 - 14.410
80	86.1 ± 5.2	74.9 ± 6.8	0.000	11.200	6.693 - 15.707
85	85.8 ± 5.6	73.7 ± 6.2	0.000	12.133	7.704 - 16.562
90	86.1 ± 5.1	74.3 ± 5.8	0.000	11.800	7.733 - 15.867
95	86.4 ± 5.5	77.1 ± 7.2	0.000	9.267	4.454 - 14.080
100	86.5 ± 6.4	82.0 ± 6.9	0.078	4.467	-0.526 - 9.460
105	86.0 ± 5.9	88.9 ± 7.2	0.243	-2.867	-7.795 - 2.062

[a]After DEX/CLO administration [b]Time of induction [c]Start of surgery

DISCUSSION

Reid and Brace[9] first described the hemodynamic response that occurs during laryngoscopy and intubation in the form of elevated blood pressure, tachycardia, coughing reflex, increased intracranial, and increased intraocular pressure. The perioperative stress associated with surgery and anesthesia results in an endocrine response that stimulates the sympathetic nervous system, where plasma adrenaline concentration will increase as arterial pressure, heart rate, and O_2 consumption increase. This adverse hemodynamic response can affect the outcome of the patient. Thus, attention

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Table 3 HR comparison based on both groups

HR	Groups		p-value	Mean difference	CI (95%)
	DEX (n=15)	CLO (n=15)			
Baseline	85.0 ± 6.7	79.7 ± 5.6	0.025	5.333	0.715 - 9.951
5	82.3 ± 4.5	70.2 ± 6.3	0.000	12.067	8.006 - 16.128
10[a]	80.5 ± 4.5	68.5 ± 6.5	0.000	12.000	7.822 - 16.178
15[b]	79.9 ± 4.2	67.7 ± 5.4	0.000	12.133	8.517 - 15.750
20	79.0 ± 4.6	67.1 ± 7.5	0.000	9.933	5.290 - 14.576
25	77.7 ± 4.8	70.7 ± 7.3	0.004	7.067	2.455 - 11.678
30[c]	75.9 ± 5.0	66.3 ± 7.0	0.000	9.533	4.968 - 14.099
35	75.5 ± 5.5	65.7 ± 5.1	0.000	9.800	5.839 - 13.761
40	74.3 ± 4.5	66.1 ± 4.8	0.000	8.200	4.709 - 11.691
45	74.0 ± 4.3	69.2 ± 5.3	0.011	4.800	1.190 - 8.410
50	74.1 ± 6.5	67.7 ± 6.7	0.013	6.333	1.421 - 11.246
55	72.3 ± 5.2	67.2 ± 6.1	0.019	5.133	0.893 - 9.373
60	72.4 ± 5.6	67.1 ± 6.4	0.022	5.333	0.831 - 9.373
65	72.6 ± 5.2	68.9 ± 6.4	0.028	3.667	-0.719 - 8.052
70	72.5 ± 5.9	67.3 ± 6.5	0.032	5.133	0.477 - 9.790
75	72.3 ± 7.4	69.1 ± 7.4	0.247	3.200	-2.345 - 8.745
80	72.3 ± 7.0	70.3 ± 7.5	0.473	1.933	-3.509 - 7.375
85	71.5 ± 6.8	70.6 ± 5.8	0.711	0.867	-3.879 - 5.613
90	72.0 ± 6.1	69.1 ± 6.4	0.219	2.867	-1.808 - 7.541
95	70.9 ± 6.5	70.3 ± 6.5	0.802	0.600	-4.256 - 5.456
100	71.3 ± 6.7	71.9 ± 7.1	0.833	-0.533	-5.671 - 4.604
105	72.2 ± 6.2	74.7 ± 7.1	0.305	-2.533	-7.502 - 2.435

[a]After DEX/CLO administration [b]Time of induction [c]Start of surgery

to the response is essential to reduce perioperative morbidity and mortality.

Arora[10] and Wijeysundera[11] reported that a temporary increase in heart rate within 3-5 minutes of dexmedetomidine administration would be followed by a decrease in heart rate, possibly because the vasoconstriction effect occurs earlier than the central sympathetic response. Scheinin[12] showed that dexmedetomidine reduces the cardiovascular response to laryngoscopy and intubation by measuring catecholamine concentrations and found that noradrenaline concentrations in plasma are less in the dexmedetomidine group in all induction phases.

In our observations, we found significant differences in the MAP between the dexmedetomidine and clonidine groups after the administration of the loading dose of the alpha-2 agonists (95.3±4.8 vs. 84.1±6.9, p <0.001) and upon induction (93.5 ± 4.6 vs. 92.9±7.5, p <0.001), all in favor to the dexmedetomidine group. These significant differences in the MAP then rose again in minutes 35-95.

The significant differences in heart rate were found after the administration of the loading dose of the alpha-2 agonists (80.5±4.5 vs. 68.5±6.5), upon induction (79.9±4.2 vs. 67.7±5.4), and upon intubation (79.0±4.6 vs. 67.1±7.5), all in favor to the dexmedetomidine group. The significant differences in heart rate went on until minute 70.

Clonidine and dexmedetomidine are both α_2 agonists that vary in terms of potential and affinity for different types of α_2 receptors. Clonidine has a specificity of 220:1 (α_2: α_1), whereas dexmedetomidine of 1620:1.[5] Dexmedetomidine is a pharmacologically active dose of medetomidine, a total agonist of the α_2 adrenergic receptor.

Clonidine is used to decrease the systemic blood pressure through central brain stem adrenergic stimulation. Clonidine is rapidly and almost entirely absorbed after oral administration, and may show a temporary increase in blood pressure after the initial dose due to mild stimulation of the peripheral post-junctional α_1 receptor.[6,13]

Dexmedetomidine shows biphasic blood pressure response in a dose-dependent manner.[14] A low dose of intravenous infusion results in a reduction of mean arterial pressure due to selectivity for central and peripheral α_2 receptors. This leads to

a decrease in heart rate and systemic blood vessel resistance indirectly decreases cardiac output and systolic blood pressure. While high doses of intravenous infusion or rapid intravenous bolus administration may lead to systemic hypertension due to the activation of peripheral α_1 post-junctional adrenergic receptors.

Dexmedetomidine loses the selectivity of α_2 receptors as dosage increases through intravenous bolus injection or rapid infusion. This loss of selectivity results in an initial increase in blood pressure and decreased heart rate simultaneously, which returns normally within 15 minutes.[15] Hypertension can also be observed because of the temporary activation of peripheral α_{2B} receptors at the time of rapid bolus injection of the drug. This brief increase in blood pressure may be due to the remarkable effects of competition with the vasodilatory effects of the central α_{2A} receptor.[16] These effects help modulate the stress response, increase the stability, and can protect against radical fluctuations in intraoperative cardiovascular parameters.

CONCLUSION

We found significant differences in hemodynamic stability in both groups, where both dexmedetomidine and clonidine were used as an adjuvant in anesthesia. Dexmedetomidine provides better MAP and heart rate stability than clonidine in patients undergoing spine surgery.

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