DEXMEDETOMIDINE AS AN ADJUNCT IN POSTOPERATIVE ANALGESIA FOLLOWING CARDIAC SURGERY- A RANDOMISED, DOUBLE-BLIND STUDY

Sarat Babu Chevuri[1], Mazharulla Khan[2], Jayashree[3]

[1]Professor, Department of Anaesthesia, Deccan College of Medical Sciences, Hyderabad.
[2]Tutor, Department of Anaesthesia, Deccan College of Medical Sciences, Hyderabad.
[3]Associate Professor, Department of Anaesthesia, Deccan College of Medical Sciences, Hyderabad.

ABSTRACT

BACKGROUND

Dexmedetomidine has anxiolytic, sedative and analgesic properties, which is widely used as an adjuvant during general anaesthesia. Use of dexmedetomidine as an anaesthetic adjuvant during cardiac surgery decreased the incidence of delirium, possibly by sparing the consumption of general anaesthetics. Evidence in this aspect was still lacking.

The aim of this study was to determine analgesic efficacy of dexmedetomidine used as a continuous infusion without loading dose in post-cardiac surgery patients.

MATERIALS AND METHODS

A prospective, randomised, double-blind clinical study in a single tertiary care hospital on patients posted for elective cardiac surgery under cardiopulmonary bypass. Sixty-four patients who underwent elective cardiac surgery under general anaesthesia were shifted to intensive care unit (ICU) and randomly divided into two groups. Group A (n= 32) received a 12 h infusion of normal saline and Group B (n= 32) received a 12 h infusion of dexmedetomidine 0.4 µg/kg/h. Postoperative pain was managed with intravenous bolus of fentanyl. Total fentanyl consumption, haemodynamic monitoring, Visual Analogue Scale (VAS) pain ratings and Ramsay Sedation Scale were charted every 6th hour for 24 h postoperatively and followed up till recovery from ICU. Student's t-test, Chi-square/ Fisher's exact test has been used to find the significance of study parameters between the groups.

RESULTS

Dexmedetomidine treated patients had significantly less VAS score at each level ($P < 0.001$). Total fentanyl consumption in dexmedetomidine group was (118.13 ± 35.78 µg) than in saline group (190.56 ± 36.99 µg) with $P < 0.001$. A statistically significant but clinically unimportant sedation was noted at 6 and 12 h ($P < 0.001$ and $P = 0.046$, respectively). Incidence of delirium was less in dexmedetomidine group ($P = 0.086$ +). Haemodynamic parameters were statistically insignificant.

CONCLUSION

Dexmedetomidine infusion even without loading dose provides safe, effective adjunct analgesia, reduces narcotic consumption, and showed a reduced trend of delirium incidence without undesirable haemodynamic effects in the cardiac surgery patients.

KEYWORDS

Cardiac Surgery, Dexmedetomidine, Postoperative Pain.

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BACKGROUND

Dexmedetomidine has a comparatively high ratio of α2/α1-activity (1620: 1 as compared with 220: 1 for clonidine) and therefore is considered a full agonist of the α2 receptor.[1] This may result in more effective effects of sedation without unwanted cardiovascular effects from α1 receptor activation. In contrast to the gamma-aminobutyric acid agonists and opiates, dexmedetomidine has a unique mechanism of action. It combines sedative, anxiolytic, sympatholytic, anti-delirious and analgesic sparing properties with least respiratory depression.[2,3] While no single agent has all the desirable properties of an ideal agent, an ideal strategy is to provide effective analgesia, anxiolysis and reduce the risk of delirium and agitation with minimal cardiorespiratory depression.[4]

Loading dose of 1 µg/kg over 10 - 20 mins is recommended in practice. In a study of 66 post-surgery patients receiving this loading dose, 11 out of 18 unwanted haemodynamic effects (mean arterial pressure < 60 mmHg or heart rate < 50 beats/min) occurred during loading.[5] A reduction in loading dose was recommended following a study in medical patients, especially if other sedative agents had been used prior to starting dexmedetomidine.[3]

The aim of the present study is to determine the analgesic efficacy of dexmedetomidine as a continuous

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Corresponding Author:
Dr. Jayashree,
No. 201, KBR, Sai Akshay Residency,
Opp. Ahobila DD Colony, Shivam Road, Hyderabad.
E-mail: jayashreeumesh40@gmail.com
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infusion without loading dose in post-cardiac surgery patients.

MATERIALS AND METHODS

This is a randomised double-blind study conducted from October 2016 to October 2017. At Deccan College of Medical Sciences, Hyderabad. The Hospital Ethics Committee approved this study and written informed consent was obtained from all the patients.

Inclusion Criteria

Patient's age greater than 18 years, elective cardiac surgery using cardiopulmonary bypass (CPB) including coronary artery bypass graft, valve surgery and atrial septal defect closure were included.

Exclusion Criteria

Patients with elevated serum creatinine, ejection fraction <40%, arrhythmias, deranged hepatic function and known allergy to current medication were excluded.

Apart from the study drug, all other management was according to unit protocols. All patients received a standard premedication oral gabapentin 600 mg 45 mins before shifting to operating room and general anaesthesia consisted of midazolam 0.1 mg/kg, fentanyl 10 µg/kg, propofol 100 ug/kg/min and vecuronium 0.2 mg/kg.

All patients were monitored with routine cardiac surgery haemodynamic monitoring. All patients were operated under normothermic non-pulsatile CPB.

Study Protocol- Sixty-four patients scheduled for elective cardiac surgery consented to participate in the study. After surgery patients were shifted, intubated and ventilated to a cardiothoracic intensive care unit (ICU) and then were prospectively randomised in a double-blind fashion into one of the two groups using computer.

Group A (n= 32) received a 12 h infusion of normal saline and Group B (n= 32) received a 12 h infusion of dexmedetomidine 0.4 µg/kg/h without a loading dose.

Postoperative pain was supplemented with intravenous fentanyl 25 µg intermittent bolus, whenever the Visual Analogue Scale (VAS) pain score was more than 5. Total fentanyl consumption, haemodynamic monitoring, VAS pain rating and Ramsay Sedation Scale (RSS) were charted every 6th hourly for 24 h postoperatively and followed-up till recovery from ICU. Richmond Agitation Sedation Scale (RASS) was used to categorise delirium.

Statistical Analysis- Results on continuous measurements are presented as mean ± standard deviation and results on categorical measurements are presented in a number (%). Significance is assessed at 5% level of significance. Student's t-test (two-tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups and Chi-square/ Fisher's exact test has been used to find the significance of study parameters on categorical scale between two or more groups. About 95% confidence interval has been computed to find the significant features.[6]

The statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment version 2.11.1 were used for the analysis of the data. Microsoft Word and Excel have been used to generate graphs, tables etc.

RESULTS

A prospective, randomised, double-blind clinical study was done in a single tertiary care hospital on patients posted for elective cardiac surgery under cardiopulmonary bypass. Sixty-four patients who underwent elective cardiac surgery under general anaesthesia were shifted to intensive care unit (ICU) and randomly divided into two groups. Group A (n=32) received a 12 h infusion of normal saline and group B (n=32) received a 12 h infusion of dexmedetomidine 0.4 µg/kg/h.

Variable	Group A (n= 32)	Group B (n= 32)	P value
Age in Years	41.8 ± 11.9	45.3 ± 14.7	0.2992
Gender Male: Female	16:16	17:15	1.000
Weight (kg)	52.7 ± 8.7	54.7 ± 9.07	0.3715
Height (cm)	153.1 ± 10.1	153.4 ± 8.9	0.90

Table 1. Patient Demographic Data

There were no statistically significant differences between patient demographics and types of surgery (Table 1) and intraoperative bypass time (CPB), aortic cross-clamp time, duration of surgery and fentanyl consumption (Table 2).

Variable	Group A (n= 32)	Group B (n= 32)	P value
CPB (min)	96.00±36.51	99.22±31.61	0.7073
AOX (min)	67.63±23.52	68.00±20.05	0.9462
DOS (min)	192.16±38.82	198.5±37.48	0.5089
Fentanyl (µg)	830.25±137.98	825.56±120.46	08853

Table 2. Intraoperative Data

CPB: Cardiopulmonary bypass; AOX: Aortic cross-clamp time; DOS: Duration of surgery.

VAS Score	Group A (n= 32)	Group B (n= 32)	P value
0 h	4.85 ± 1.28	3.12 ± 0.69	<0.001
6 h	5.55 ± 1.04	4.44 ± 0.90	<0.001
12 h	5.44 ± 1.07	4.13 ± 1.02	<0.001
18 h	5.11 ± 0.99	4.31 ± 1.14	0.038
24 h	5.20 ± 0.71	4.85 ± 0.88	0.022

Table 3. Comparison of VAS Score in Postoperative Period

Dexmedetomidine treated patients had a statistically significant less VAS score of pain 3.12 ± 0.69, 4.44 ± 0.90, 4.13 ± 1.02, 4.31 ± 1.14 and 4.85 ± 0.88 at 0, 6, 12, 18 and 24 h respectively (Table 3). Fentanyl consumption in the first 24 h was less in dexmedetomidine group (118.13 ± 35.78 µg) than in saline group (190.56 ± 36.99 µg) with P < 0.001 (Table 4).

Variable	Group A	Group B	P value
Total fentanyl (µg)	190.56 ± 36.99	118.13 ± 35.78	< 0.001
Delirium in number (%)	5 (15.6)	1 (3.1)	0.086 +

Table 4. Comparison of Total Fentanyl use and Incidence of Delirium in the Postoperative Period

RSS Score	Group A (n = 32)	Group B (n = 32)	P value
0 h	2.71 ± 0.47	2.71 ± 0.64	1.000
6 h	2.11 ± 0.42	2.90 ± 0.67	<0.001
12 h	2.03 ± 0.18	2.19 ± 0.4	0.046
18 h	2.01 ± 0.00	2.01 ± 0.00	-
24 h	2.01 ± 0.00	2.01 ± 0.00	-

Table 5. Comparison of RSS in the Postoperative Period

A statistically significant but clinically unimportant sedation was noted at 6 h (RSS of 2.90 ± 0.67, P < 0.001) and 12 h (RSS of 2.19 ± 0.4, P = 0.046) (Table 5). A reduced trend in delirium incidence was noted in dexmedetomidine group (3.1%) than in saline group (15.6%) with P = 0.086 + (Table 4). Awakening time and haemodynamic parameters in postoperative period was statistically insignificant (Tables 6 and 7).

Variable	Group A	Group B	P value
Awakening time (min)	122.59 ± 51.47	123.84 ± 46.17	0.919

Table 6. Awakening Time in the Postoperative Period

Haemodynamic Variable	Time	Group A	Group B	P value
Pulse rate (beats/min)	0 h	88.44 ± 12.91	85.94 ± 10.31	0.3953
	6 h	87.31 ± 11.38	84.93 ± 8.75	0.353
	12 h	87.06 ± 7.73	85.81 ± 6.71	0.492
	18 h	89.18 ± 9.34	87.68 ± 8.69	0.509
	24 h	87.93 ± 11.12	85.94 ± 9.50	0.442
Mean BP (mmHg)	0 h	74.25 ± 3.76	75.56 ± 4.10	0.187
	6 h	74.31 ± 5.25	75.13 ± 4.59	0.512
	12 h	75.06 ± 4.47	75.43 ± 3.83	0.720
	18 h	73.50 ± 3.59	74.75 ± 3.99	0.193
	24 h	74.37 ± 3.85	76.87 ± 6.12	0.155

Table 7. Comparison of Pulse and Mean BP in the Postoperative Period

DISCUSSION

Dexmedetomidine is the dextro-stereoisomer and active ingredient of medetomidine, an agent used for many years in veterinary anaesthesia. It is a highly selective α2 agonist with an affinity 8 times that of clonidine for the adrenoceptor.[7]

Dosage- The majority of adverse events (hypotension and bradycardia) occur as a result of the loading dose of dexmedetomidine. This was expected from the known properties of α2 agonists and might have been avoided by omitting the loading dose and beginning the infusion while in the operating theatre. The protocol allowed neither boluses of study drug nor exceeding the maximum infusion rate (0.7 µg/kg/h dexmedetomidine). The hypotension and bradycardia occurring during the loading dose phase of the dexmedetomidine was only seen in cardiac patients. This is probably directly attributable to stimulation of the central postsynaptic α2 receptors causing inhibition of sympathetic activity or augmentation of parasympathetic activity.[5]

Hall et al demonstrated in a randomised, double-blinded study involving small population of volunteers with healthy cardiovascular systems that small doses (0.2 and 0.6 µg/kg/h infusions, small and moderate doses, respectively) of dexmedetomidine provided significant sedation and analgesia to the conventional pain therapy. Cardiovascular stability and respiratory function were both well maintained.[8] In a randomised controlled trial in 306 cardiac surgery patients showed that dexmedetomidine at a median dose of 0.49 µg/kg/h provided effective sedation and targeted analgesia without an increase in hypotension or vasopressor requirements. In addition, dexmedetomidine treatment significantly reduced the duration of delirium and promoted early extubation when compared with morphine based regimen.[9]

In our study, we used dexmedetomidine at 0.4 µg/kg/h without a loading dose in the immediate postoperative period after cardiac surgery, which had residual sedative and analgesic effects.

Haemodynamics- Venn et al reported an incidence of 27% significant haemodynamic changes of which 61% occurred during the loading dose phase with some patients being withdrawn from the study as a result.[5]

Ickeringill et al showed a reduction of 8% in heart rate and 10% in systolic blood pressure from baseline after the initiation of dexmedetomidine without a loading dose. None of their patients had a clinically significant bradycardia and only six patients (12%) required the introduction of a pressor for management of low blood pressure. Though, the absence of a control group makes it difficult to discover a

direct cause and effect in this group of patients where considerable fluid shifts, blood loss and dynamic changes are likely to be occurring in the postoperative period. Postoperative warming in the cardiac surgery group and the concurrent use of inotropes and pressors may mask the true effect on blood pressure. They demonstrated that by avoiding a loading dose of dexmedetomidine, unnecessary cardiovascular effects can be significantly minimised.[10]

In our study, there were no significant haemodynamic changes in the dexmedetomidine group when compared to the saline group. So by omitting a loading dose of dexmedetomidine, unwanted cardiovascular effects were avoided.

Analgesia and Sedation- Ickeringill et al studied in postsurgical patients without loading dose and found that 76% required no rescue sedation and 48% required no rescue analgesia. Of those requiring rescue analgesia, only 7 (14%) required significant additional analgesia. Cardiac group required the least additional sedation and/ or analgesia.[10]

Shahbaz et al concluded that administration of dexmedetomidine before the completion of major surgical procedures associated with above-average postoperative pain significantly reduced by 66%, the early postoperative need for morphine and was associated with slower HR and PACU.[11]

Venn et al conducted a study including 98 patients with complete data, 47 received dexmedetomidine and 51 received placebo. Eighty-one patients (83%) underwent cardiac surgery requiring CPB. There were no overall differences in the distribution of Ramsay Sedation Scores between the dexmedetomidine and placebo groups while intubated.[5]

Our study correlated well with the previous studies. We demonstrated that dexmedetomidine treated patients appreciated less pain and analgesic requirement throughout the postoperative period. There was statistically significant sedation in study group at 6 and 12 h when compared to the control group, although this was not significant clinically.

Delirium- We used RASS to define delirium. RASS has good reliability and validity and is increasingly recommended for use, though many others are also used.[12]

Although, the exact mechanism by which dexmedetomidine counteracts agitation remains unclear, animal models show an increase in acetylcholine and reduction in noradrenaline levels in cerebrospinal fluid in response to dexmedetomidine suggesting a central nervous system mediated effect.[13]

In a comparative study with lorazepam, dexmedetomidine infused for longer than 24 h up to 1.5 µg/kg/h in ventilated critically ill patients noticed a significant reduction in delirium and number of days in coma.[14] Dexmedetomidine has also been successfully used in the management of emergence delirium after failure of conventional therapy in a cohort of critically ill mechanically ventilated patients.[13] In this study, the average dose used was 0.79 µg/kg/h and resulted in 86% of patients achieving a target Motor Activity Assessment Scale within 12 h. Similar results were shown in 111 patients treated for emergence delirium as assessed using the Ramsay Sedation Score.[15]

A recent randomised pilot study demonstrated the superiority of dexmedetomidine over haloperidol in the treatment of agitated delirious ventilated ICU patients.[16] A well-conducted multicentre randomised double-blind controlled trial has compared dexmedetomidine with midazolam in ventilated medical and surgical ICU patients for longer than 24 h. There was a 22.6% absolute reduction in the incidence and 48% reduction in the duration of delirium achieved with dexmedetomidine compared to midazolam in all patients and in patients who were delirious at enrolment.[17]

Yapici et al evaluated the use of dexmedetomidine to facilitate the weaning of delirious postoperative patients from mechanical ventilation. They concluded that dexmedetomidine may help to eliminate the emergence of agitation and can be a good treatment choice for the delirium state after cardiac surgery.[18]

In a meta-analysis of nine studies by Lin et al, the most striking finding was that sedation with dexmedetomidine is associated with lower risk of delirium following cardiac surgery. Dexmedetomidine could be a safe and efficacious sedative agent in cardiac surgery patients.[19]

Though our study was aimed to study delirium, dexmedetomidine treated patients had reduced the incidence of delirium (3.1%), while it was 15.6% in the control group.

CONCLUSION

Dexmedetomidine infusion even without loading dose provides safe, effective adjunct analgesia, reduces narcotic consumption and showed a reduced trend of delirium incidence without undesirable haemodynamic effects in the cardiac surgery patients.

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