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A Comparative Study of Different Doses of Dexmedetomidine in Attenuating Hemodynamic Response in Patients Undergoing Laparoscopic Cholecystectomy.

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Conflicts of Interest: Nil.

Abstract

Background and Aims: Most adverse incidents that follow the use of dexmedetomidine, occur during or after administration of a loading dose of the drug. Reducing or omitting the loading dose could result in decreasing the incidence and severity of these adverse events. The aim of this study is to compare the hemodynamic effects of two different doses of dexmedetomidine in patients undergoing laparoscopic cholecystectomy.

Methods: It was a randomized prospective single blind study. After institutional ethical clearance, 90 patients of ASA Physical status I and II were enrolled in the study and divided into two groups. Group L received dexmedetomidine at a loading dose of 1mcg/kg over 10 minutes followed by 0.4mcg/kg/hr. Group M received a continuous infusion of dexmedetomidine at 0.5mcg/kg/hr. The general anesthesia technique was standardized for both the groups. The primary outcome measures were hemodynamic response intra operatively. The secondary outcome measures were to note down any adverse effects associated with the different doses of drugs and to compare post-operative sedation scores between the two groups. The statistical package used was SPSS.

Results: Both groups were well matched for their demographic data. There was no statistically significant difference ($P < 0.05$) between the two groups in heart rate, systolic, diastolic and mean arterial pressures at all time points. Sedation scores were more in group L. 23 and 12 patients in group L had incidence of bradycardia and hypotension respectively. Number of incidents of bradycardia and hypotension in group M were 11 and 8 respectively. None of the patients in any group had any serious adverse effects.

Conclusion: Since dexmedetomidine at continuous infusion of 0.5mcg/kg/hr offers almost similar hemodynamic characteristics to that of a loading dose of 1mcg/kg over 10 minutes followed by 0.4mcg/kg/hr, and has a lower incidence of adverse effects, it can be a safer and more cost-effective alternative.

Key words: Anesthesia, dexmedetomidine, general, intubation, laryngoscopy.

Introduction

Dexmedetomidine is a centrally acting, highly selective -2 adrenoceptor agonist, which produces sedative and analgesic effects without causing significant respiratory depression [1-5].

It lowers the tachycardic response to endotracheal intubation and assures a greater hemodynamic stability during the intraoperative period. It has the ability to potentiate the anesthetic requirements for opioids as well as volatile and regional agents [6]. It also produces an anesthetic-sparing effect [7].

The most frequently observed adverse events include hypotension, hypertension, nausea, bradycardia and atrial fibrillation [8]. Most of these events occur after or during the loading dose, therefore, reducing or omitting the loading dose could result in decreasing their incidence and severity [9].

Yeom [10] found that Dexmedetomidine at a loading dose of 1 μg/kg for 10 min, and a maintenance dose of 0.5 μg/kg/h may induce excessive sedation, airway obstruction, and/or coughing under spinal anesthesia for lower extremity surgery.

Further studies to determine a lower loading and/or maintenance dose are needed to reduce side effects.

We aimed to compare the efficacy of a continuous infusion of dexmedetomine at 0.5mcg/kg/hr to that the standard regimen of a loading dose of 1mcg/kg over 10 mins followed by a maintenance dose of 0.4mcg/kg/hr in attenuating the hemodynamic response in patients undergoing laparoscopic cholecystectomy under general anesthesia.

Methods

This single blinded randomised controlled prospective parallel designed clinical trial was planned with Patients undergoing laparoscopic cholecystectomy under general anesthesia in VIMSAR, Burla; following CONSORT guidelines for clinical trials. Based on a pilot study, to get a clinically significant difference between the groups, the necessary sample size was estimated using sample size and power calculations developed by William D. Dupont and licensed under a Creative Commons Attribution-Non Commercial-No Derivs 3.0 United States License. A sample size of 40 subjects in each group was required to reject the null hypothesis that both doses are equally efficacious. It was estimated considering 5% type I error and 20% type II error. Considering a 10% dropout rate, the sample size for each group came to be 44. So we enrolled 45 patients to each group

Ethical clearance for the study was obtained from the Institutional Ethical Committee and instruments were standardized prior to commencement of the study.

Simple random sampling was done for recruitment of subjects (45 in each group) into the study following Inclusion Criteria: Age 20-60 years of both sexes with ASA Grade I & II, Mallampatti Grade I & II. Patients with associate comorbidities like hypertension, diabetes, cardiovascular, hepatic or renal disease, Pregnancy & Lactation, Patients with psychiatric disorders, History of allergy to dexmedetomidine or clonidine, Patients on β-blockers, antidepressants, anxiolytics, anticonvulsant or antipsychotics, Mallampatti Grade III or higher, Patients in whom laryngoscopy time exceeded 15 s and Patients with baseline HR <60/min were excluded from the study.

Then Patients were divided into two groups and subjects of both groups were matched by one to one method according to age, sex and weight. On arrival to operating room, NIBP, ECG, Pulse oximeter, and BIS index monitor was attached and initial values of all parameters were noted. IV line was secured and dexmedetomidine infusion was started using a B. Braun Melsungen AG Perfusor® Space syringe pump according to following protocol:

a. Group L (n=45): Loading dose of 1mcg/kg over 10 mins followed by maintenance dose of 0.4 mcg/kg/hr.

b. Group M (n=45): Continuous infusion at 0.5 mcg/kg/hr.

5 mins after starting infusion of dexmedetomidine, the subjects of both groups were premedicated with inj.

Midazolam 0.05mg/kg iv and inj. nalbuphine 0.3 mg/kg iv. Preoxygenation with 100% O2 was done. Subjects were induced with Propofol 2mg/kg iv and Vecuronium 0.1mg/kg iv loading dose for neuromuscular blockade was given. Subjects were intubated with appropriate sized cuffed endotracheal tube 3 mins after vecuronium administration. Maintenance was done with nitrous oxide and oxygen in 2:1 ratio. Isoflurane was started at 0.6 % and was adjusted to keep the BIS score in the range of 40-60. Muscle relaxation was maintained using 0.04 mg/kg top up doses of vecuronium.

HR, BP and SPO2 were noted down at the following times:

T0 = baseline, before starting dexmedetomidine

T1 = After premedication

T2 = After induction

T3 = Immediately after intubation

T4 = 3 mins after intubation

T5 = 5 mins after intubation

T6 = After laryngoscopy for extubation

T7 = 10 mins after extubation

Incidence of hypotension, defined as SBP <80 mm of Hg or 20% decrease in MAP from baseline, was noted in both the groups. Hypotension was treated with 6mg iv ephedrine. Incidence of bradycardia defined as HR <50/min was noted in both groups. Bradycardia was treated with 0.6mg iv atropine. An increase in HR and/or mean arterial pressure (MAP) >20% from baseline values was treated by increasing the initial isoflurane concentration by 0.2% increment every 4 min up to a maximum of 1% end-tidal concentration. Incidence of serious adverse effects like arrhythmias, AV block, Cardiac arrest, atrial fibrillation, and T-wave inversion was noted in both the groups.

Infusion of dexmedetomidine was stopped at the end of laryngoscopy and suctioning before extubation. Reversal of neuromuscular blockade was done using neostigmine 2.5mg iv and glycopyrrolate 0.5mg iv. All parameters were recorded immediately, 5 mins and 10 mins after extubation. The degree of sedation was assessed using the 6-point Ramsay sedation scale [12]:

a. 1 = Anxious or agitated and restless or both.

b. 2 = Cooperative, oriented and tranquil.

c. 3 = Drowsy but responds to commands.

d. 4 = Asleep, brisk response to light glabellar tap or loud auditory stimulus.

e. 5 = Asleep, sluggish response to light glabellar tap or loud auditory stimulus.

f. 6 = Asleep and unarousable.

Sedation score >3 was considered an undue sedation [13]. After adequate recovery, patients were shifted to post-anaesthesia care unit and monitored for 12 h and later shifted to ward.

Statistical analysis was done using RStudio v1.0.1 software package (RStudio, Inc. 250 Northern Avenue Suite 410 Boston, Massachusetts 02210). HR, SBP, DBP and MAP were compared using Independent t-test. Sedation scores were compared using Fisher Exact test. P value <0.05 was considered statistically significant.

Results

The groups were well matched for their demographic data and duration of surgery (Table 1). The basal readings of HR, SBP, DBP and MAP were similar in both the groups. A comparison between heart rates of both groups (Table 2) showed lower overall heart rates in Group L, but the difference was not statistically significant. On comparing the systolic blood pressures (Table 3), SBP was significantly lower in Group L, 5 mins after intubation. The difference at rest all times was insignificant. Table 4 compares the diastolic blood pressures at various times. It was significantly lower in Group L immediately after intubation. The difference was statistically insignificant at

other points. Mean Arterial Pressure was significantly lower in Group L immediately after intubation (Table 5). The difference was statistically insignificant at other points. Bradycardia was observed in 23 patients of group L and 11 in group M. Hypotension was observed in 12 patients in Group L and 8 patients in group M (Table 6). The Ramsay sedation scores for both the groups 10 mins after extubation were compared (Table 7). In Group L, Ramsay score was 2 for 15, 3 for 26 and 4 for 4 patients respectively. In group M, it was 2 for 24 and 3 for 21 patients respectively. (P value <0.01). In none of the patients of any group did the SpO2 fall below 95%. None of the patients in any of the group needed oxygen supplementation.

Discussion

Dexmedetomidine acts through three types of α2 receptors‑α2 A, α2 B and α2 C situated in brain and spinal cord. The resultant action is sedation, anxiolysis, analgesia and sympatholysis, the latter leading to hypotension and bradycardia. Activation of α2 A receptors in brain stem vasomotor center results in suppression of norepinephrine release, hypotension and bradycardia.

Dexmedetomidine has been evaluated in the past to assess its effect on hemodynamic responses in patients undergoing laparoscopic surgeries. The molecule has been used in infusion form with or without bolus dose. Infusion rates varying from 0.1 to 10 mcg/kg/h [9,10,11] have been studied. However, with higher dose infusion of dexmedetomidine, high incidence of adverse cardiac effects has been observed. [11]

A biphasic response on blood pressure occurs with a bolus dose. [6] Initially, there occurs hypertension followed by fall in blood pressure. This response is seen often more in young and healthy patients. [12] Stimulation of α2 B receptors in vascular smooth muscles is said to be responsible for this. Low dose infusion of 0.25–0.5 mcg/kg/h results in a monophasic response of 10–15% fall in mean arterial blood pressure and PR. [6] Furthermore, in low dose, dexmedetomidine exhibits linear kinetics.

Manne et al [13] had found that dexmedetomidine low dose (0.4 mcg/kg/hr) infusion without any bolus dose reduced the hemodynamic stress response to intubation, pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy without any significant adverse effects. Sebastian et al [14] found that there was no significant difference in hemodynamic parameters when dexmedetomidine was used in doses of 0.75 mcg/kg/hr and 0.5mcg/kg/hr. Jarineshin et al [15] found that 0.5 μg/ kg of dexmedetomidine properly decreases cardiovascular responses and a significant difference was not observed between 0.5 - 1 μg/ kg of dexmedetomidine in reducing HR and MAP. Our study results correlate with these findings.

Dexmedetomidine in a dose of 1 μg/kg has been shown to cause increased sedation levels and need for oxygen supplementation by few authors. [13,16,17] in our study we found that sedation scores were greater in patients receiving a loading dose.

Incidence of bradycardia and hypotension were higher in Group L which may be attributed to the use of a loading dose.

There were few limitations of our study. Invasive blood pressure monitoring was not used which would have provided us a better comprehension giving us beat-to-beat recording of the parameters. This was not performed due to cost constraints. Plasma catecholamine level monitoring was not performed due to the limited facilities available at our set-up. This could have comprehensively concluded the usefulness of dexmedetomidine.

Conclusion

Dexmedetomidine at continuous infusion of 0.5mcg/kg/hr offers almost similar hemodynamic characteristics to that

of a loading dose of 1mcg/kg over 10 minutes followed by 0.4mcg/kg/hr, and has a lower incidence of adverse effects in patients undergoing laparoscopic cholecystectomy. So, using a lower dose is a safer and cost-effective alternative.

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Tables and Figures

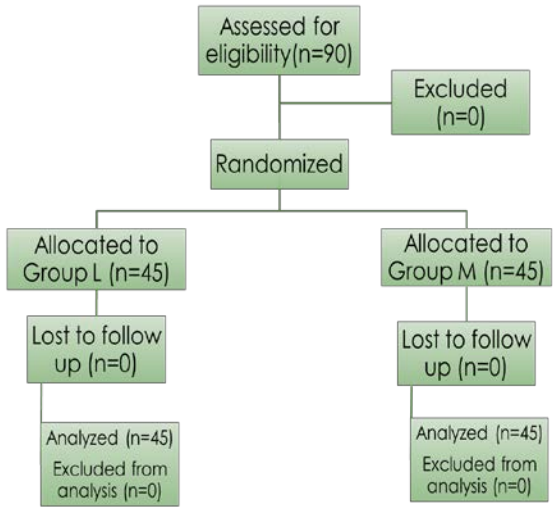

Figure 1. CONSORT Diagram

Table 1. Demographic Details and Duration Of Surgery

Groups	Mean Age (years) +/- SD	Male (%)	Female (%)	Mean Weight (Kg) +/- SD	Mean Duration of Surgery (Mins) +/- SD
L	41.25 ± 7.38	11 (24%)	34 (76%)	55.25 ± 8.48	93.55 ± 12.96
M	42.05 ± 7.72	13 (28%)	32 (72%)	53.65 ± 6.31	99.05 ± 9.34
Intergroup P	0.262			0.403	0.073

Table 1. Demographic Data and Duration of Surgery

Table 2. Comparison of HR at chosen points of time

Time	Group L (Mean ± SD)	Group M (Mean ± SD)	P value
T0	85.04 ± 7.35	84.33 ± 8.21	0.779
T1	70.17 ± 6.17	71.64 ± 6.05	0.497
T2	69.80 ± 5.08	72.35 ± 7.72	0.320
T3	88.11 ± 6.43	90.73 ± 5.91	0.340
T4	68.82 ± 4.76	71.11 ± 4.65	0.290
T5	69.22 ± 5.29	72.31 ± 7.21	0.117
T6	85.44 ± 7.53	88.75 ± 6.93	0.060
T7	81.31 ± 6.84	83.66 ± 7.04	0.125

Table 2. Comparison of Heart Rates

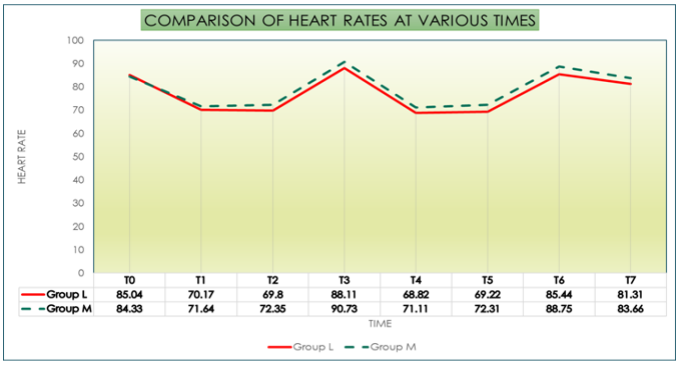

Figure 2. Comparison of Heart Rates

Table 3. Comparison of SBP at chosen points of time

Time	Group L (Mean ± SD)	Group M (Mean ± SD)	P value
T0	126.40 ± 7.62	128.37 ± 5.66	0.314
T1	121.44 ± 5.43	123.93 ± 7.51	0.283
T2	108.60 ± 6.08	111.62 ± 3.98	0.154
T3	127.11 ± 4.97	130.73 ± 4.64	0.122
T4	119.84 ± 5.77	122.02 ± 7.20	0.375
T5	**115.68 ± 6.32**	**120.95 ± 6.83**	**0.046**
T6	125.22 ± 4.86	129.66 ± 5.57	0.093
T7	124.57 ± 7.12	127.97 ± 6.27	0.122

Table 3. Comparison of SBP

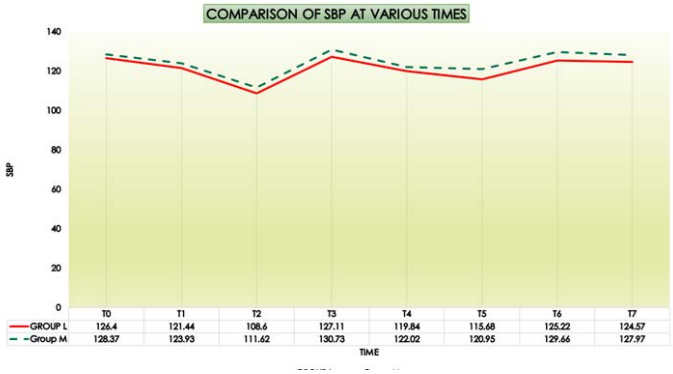

Figure 3. Comparison of SBP

Table 4. Comparison of DBP at chosen points of time			
Time	Group L (Mean ± SD)	Group M (Mean ± SD)	P value
T0	78.35 ± 5.76	80.33 ± 6.81	0.427
T1	71.51 ± 7.61	74.66 ± 5.39	0.086
T2	66.51 ± 6.45	70.17 ± 7.03	0.054
T3	**72.52 ± 7.12**	**77.42 ± 4.93**	**0.037**
T4	69.95 ± 5.20	71.86 ± 6.35	0.678
T5	69.55 ± 4.84	72.04 ± 7.18	0.132
T6	78.42 ± 6.34	79.42 ± 5.62	0.564
T7	77.04 ± 5.48	79.37 ± 6.22	0.326

Table 4. Comparison of DBP

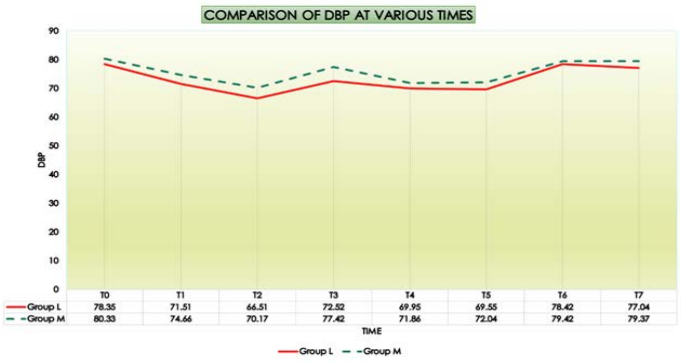

Figure 4. Comparison of DBP

Table 5. Comparison of MAP at chosen points of time			
Time	Group L (Mean ± SD)	Group M (Mean ± SD)	P value
T0	94.33 ± 8.45	96.40 ± 9.32	0.091
T1	87.17 ± 9.13	88.24 ± 11.86	0.520
T2	80.53 ± 7.75	82.24 ± 10.43	0.191
T3	**90.73 ± 8.42**	**94.06 ± 9.23**	**0.020**
T4	86.08 ± 10.21	88.12 ± 8.94	0.061
T5	84.91 ± 9.27	87.44 ± 9.70	0.138
T6	94.01 ± 8.96	94.68 ± 10.11	0.678
T7	92.82 ± 11.14	93.55 ± 9.72	0.590

Table 5. Comparison of MAP

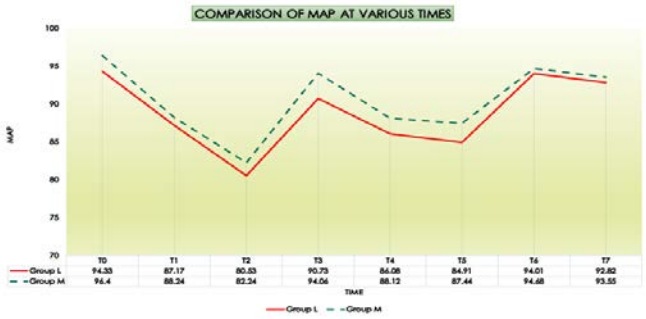

Figure 5. Comparison of MAP

Table 6. Incidence of Hypotension & Bradycardia		
Hypotension & Bradycardia	Group L (%) N= 45	Group M (%) N=45
Hypotension	12 (**26.6%**)	8 (17.7%)
Bradycardia	23 (**51.1%**)	11 (24.4%)

Table 6. Incidence of Hypotension and Bradycardia

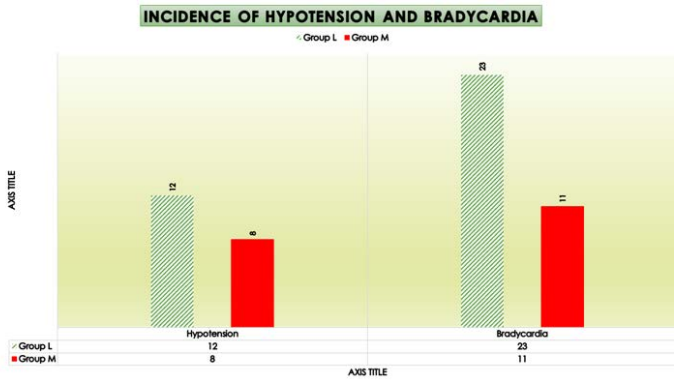

Figure 6. Incidence of Hypotension and Bradycardia

Table 7. Comparison of Sedation Scores			
Ramsay Score	Group L (%) n=45	Group M (%) n=45	P Value <0.01
1	0 (0%)	0 (0%)	
2	15 (33.33%)	24 (53.33%)	
3	26 (57.77%)	21 (46.67%)	
4	4 (8.88%)	0 (0%)	
5	0 (0%)	0 (0%)	
6	0 (0%)	0 (0%)	

Table 7. Comparison of Ramsay Sedation Scores.