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To compare the hemodynamic changes with single dose of intravenous dexmedetomidine versus midazolam: a randomized, prospective study

Abstract

Introduction: The stress produced by anesthesia and surgery may produce undesirable hemodynamic effects. Different agents have been used as preoperative medication to eliminate or suppress stress reaction. We hypothesize Dexmedetomidine provides better hemodynamic control as compared to midazolam when used as premedication for patients. In this study, we evaluated effects of pre anesthetic single dose intravenous Dexmedetomidine in a dose of 0.06 mcg/kg body weight with intravenous midazolam 0.05mg/kg body weight on haemodynamic parameters.

Methods: This prospective randomized study was conducted on 60 patients undergoing open Cholecystectomy under general anesthesia. After obtaining consent, patients were randomized into group M (received intravenous midazolam 0.05 mg/kg body weight) and group D (received intravenous Dexmedetomidine 0.6 mcg/kg body weight). The anesthetic technique was standardized for both the groups. The haemodynamic parameters recorded included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) at before start of trial drug infusion (baseline), 5 minutes after start of trial drug infusion, 10 minutes after start of trial drug infusion (end of infusion), at induction of anesthesia, at laryngoscopy and intubation, 5/10/20/30/40 minutes after laryngoscopy and intubation.

Results: The baseline parameters were comparable in both the groups ($P>0.05$). The heart rate was statistically significant between the two groups, being higher in group M as compared to group D ($p<0.05$). The blood pressures (systolic, diastolic and mean) were statistically significant after start of study drugs at all time intervals ($p<0.05$). The change in blood pressures (systolic, diastolic and mean) as compared to baseline was significantly different in group M at all time ($p<0.05$), while it was comparable after laryngoscopy in group D ($p>0.05$). Also, the blood pressures (systolic, diastolic and mean) were statistically significant between the two groups, being higher in group M as compared to group D ($p<0.05$).

Conclusion: We conclude that a single intravenous pre anesthetic dose of Dexmedetomidine of 0.6mcg/kg body weight blunts haemodynamic response of anesthetic and surgical stress more efficiently and maintain the intraoperative haemodynamic stability in comparison to 0.05mg/kg dose of midazolam.

Keywords: dexmedetomidine, midazolam, hemodynamic, pre anesthetic, single dose, intravenous

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Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; ECG, electrocardiogram; SPSS, social sciences statistical software; NIBP, non invasive blood pressure

Introduction

Obtunding the hemodynamic response to stress associated with anesthesia and surgery is a major concern in the current practice of anesthesia. Stress produced by anesthesia and surgery produce undesirable hemodynamic effects in the form of tachycardia, hypertension and increased metabolic demands by stimulation of sympathoadrenal response.[1–3] Different agents like benzodiazepines, opioids, barbiturates, antihistamines and beta-adrenoreceptor antagonists have traditionally been used as preoperative medication to eliminate or suppress stress reaction to anesthesia and surgery.[2,3] These agents have been used with different outcomes with regards to obtundation of stress response. Midazolam and Dexmedetomidine are the drugs used for obtunding stress response. Midazolam is a commonly used benzodiazepine for its early onset and short duration of action.[2,3] The hemodynamic effects of midazolam are mild reduction in systemic vascular resistance, heart rate, systemic blood pressure and claimed to maintain hemodynamic stability during the intraoperative period. Dexmedetomidine is more alpha-2 selective. Dexmedetomidine, in single pre anesthetic intravenous dose of up to 0.6 mcg/kg has been shown to reduce the anaesthetic requirement and lessen the haemodynamic response to stressful intraoperative events.[4]

We hypothesize Dexmedetomidine provides better hemodynamic control as compared to midazolam when used as premedication for patients. In this study, we evaluated effects of preanaesthetic single dose intravenous Dexmedetomidine in a dose of 0.06mcg/kg body weight with intravenous midazolam 0.05mg/kg body weight on haemodynamic parameters.

Methods

This prospective randomized study was conducted at the tertiary care institute after approval from the hospital ethics committee. The study was carried out on 60 patients undergoing open Cholecystectomy surgery under general anesthesia during the period December 2010 to November 2011. Patients in the age group of 18-60years, of both sex, ASA physical status I and II were included in the study. Patients who were having difficult airway, morbidly obese, on alpha-adrenergic blockers or beta-adrenergic blockers, patients with heart block, bradycardia, hypotension or other significant cardiovascular diseases, significant respiratory, hepatic or renal diseases, diabetes mellitus, known allergic to the study drugs or patient's refusal were excluded from the study.

The patients were visited in the ward and thorough pre-anesthetic assessment was done. Patients were explained premedication and anesthetic procedure and written consent obtained for participation in the study was taken. All patients were shifted to the pre-operative holding room at least 30minutes prior to induction of anesthesia. Peripheral venous route was accessed with 18G intravenous cannula and lactated Ringer's solution infusion started at 4mL/kg/hr. Monitoring was initiated with 5 lead electrocardiogram (ECG), automated non invasive blood pressure (NIBP), and pulse oximeter (SpO_2). The patients were allowed to rest for 10-15minutes after which baseline haemodynamic parameters and SpO_2 were recorded. Thereafter, patients were randomized using computer generated random number table into two groups of 30 patients each.

I. Group M: Received intravenous midazolam 0.05mg/kg body weight.

II. Group D: Received intravenous Dexmedetomidine 0.6 mcg/kg body weight.

The calculated amount of study drug in either group was diluted with 0.9% NaCl solution to make the final volume of 10mL and infused approximately 15minutes prior to induction of anesthesia and completed in 10minutes. The study drugs were prepared by an independent anesthesiologist who was not involved in management of the patients or for collecting any observation parameters. During infusion, heart rate (HR), systolic blood pressures (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and SpO_2 were recorded at 5minutes and 10minutes (end of infusion). Patients were also continuously monitored for respiratory depression or any other side effects or complications.

Patients were shifted to the operation table and the standardized general anesthesia technique was used in all cases. Intravenous fentanyl 1.5mcg/kg body weight was administered. Patients were pre oxygenated for 3minutes. Intravenous thiopentone in a dose sufficient to abolish eye lash reflex (3-5mg/kg) was administered followed by intravenous vecuronium 0.1mg/kg body weight to facilitate laryngoscopy and tracheal intubation. After ventilation of lungs with 100% oxygen for 3minutes, trachea was intubated with appropriate size cuffed endotracheal tube. Immediately after endotracheal intubation the endotracheal tube was connected to circle breathing system and tracheal position of the tube was confirmed by bilateral chest auscultation. Tube cuff was inflated with minimum air to occlude any leak and haemodynamic parameters; HR, SBP, DBP, MAP and SpO_2 were recorded immediately thereafter. Mainstream capnometer was connected and end-tidal carbon dioxide ($EtCO_2$) was recorded. Patients were put on controlled mechanical ventilator with tidal volume 10ml/kg and respiratory rate 12-18/min to maintain $EtCO_2$ between 30-35mmHg. Anaesthesia was maintained with nitrous oxide and oxygen (2:1) and Isoflurane (MAC 1). Isoflurane was reduced by 0.2% stepwise if systolic blood pressure decreased by 25% from the baseline. Intraoperatively ringer's lactate was continued at 2mL/kg infusion and blood loss was replaced with additional crystalloid solution 3 times the volume of blood loss or blood products as deemed necessary by the attending anesthesiologist. Injection Ketorolac 1mg/kg intramuscularly was given to all the patients before skin closure. Isoflurane was discontinued approximately 10 minutes before end of surgery, if possible. However, in all the cases it was continued till the end of study period i.e. 40 minutes from laryngoscopy and intubation. Neuromuscular block was reversed with intravenous neostigmine 50mcg/kg and glycopyrrolate 10mcg/kg bodyweight.

Intraoperative hypertension was defined as SBP > 160mmHg or increase of 25% or more from the baseline. In such a case it was planned to increase the isoflurane concentration by 0.2% every 3minutes and to supplement injection fentanyl 1mcg/kg if isoflurane concentration exceeded 1%. Intraoperative tachycardia was defined as heart rate > 100 bpm or increase of 25% or more from the baseline value. It was planned to be intervened by administering injection fentanyl 1/mcg/kg body weight, and repeat the dose in 3-5minutes if required. Hypotension was defined as SBP<90 mmHg and was planned to be treated with rapid infusion of crystalloid 250-500 mL, followed by injection ephedrine 5mg intravenously in repeated doses if SBP did not increased above 90mmHg. Bradycardia as defined as heart rate<50 bpm and it was planned to be treated with 0.5mg atropine intravenously.

The haemodynamic parameters recorded included HR, SBP, DBP and MAP. Any arrhythmias were recorded. The SpO_2 and $EtCO_2$ were also recorded. These measurements were recorded at start of trial drug infusion (baseline), 5minutes after start of trial drug infusion, 10 minutes after start of trial drug infusion (end of infusion), at induction of anesthesia, at laryngoscopy and intubation, 5/10/20/30/40minutes after laryngoscopy and intubation. The patients were also monitored for any adverse effects or complications.

Statistical analysis

The change in hemodynamic parameters to less the 10% of baseline among the groups was considered to be of clinical significance. The sample size based on this assumption came out to be 28 patients in each group. We enrolled 30 patients in each group to adjust any drop out from analysis. Data was analyzed using Statistical Package for the Social Sciences (SPSS) statistical software (16^{th} version). Student T tests, Fisher's exact test and Analysis of Variance were employed for analyzing of data.

Results

The demographic profile including age, gender and ASA physical status were comparable in the two groups ($p > 0.05$) (Table 1). The baseline heart rates, blood pressures (systolic, diastolic and mean) were comparable in both the groups ($P>0.05$). The decrease in heart rate with the administration of study drugs was observed in both the groups (Table 2). However after laryngoscopy, it remained elevated at all time interval in group M and was significant when compared from baseline ($p<0.05$). But in group D, the heart rate after laryngoscopy remained comparable with the baseline throughout the study period ($p>0.05$). Also, the heart rate was statistically significant between the two groups, being higher in group M as compared to group D ($p<0.05$).

The blood pressures (systolic, diastolic and mean) were statistically significant after start of study drugs at all time intervals ($p<0.05$) (Tables 3-5). The change in blood pressures (systolic, diastolic and mean) as compared to baseline was significantly different in group

M (i.e. less before laryngoscopy and intubation and increased after laryngoscopy and intubation) at all time ($p<0.05$), while it was comparable after laryngoscopy in group D ($p>0.05$). Also, the blood pressure (systolic, diastolic and mean) was statistically significant between the two groups, being higher in group M as compared to group D ($p<0.05$).

The SpO_2 and $EtCO_2$ remained comparable in the two groups at all point of time ($p>0.05$). In Group D, 3 patients complained of dryness of mouth during the pre-induction period. No other side effects or complication like bradycardia, hypotensive episodes, arrhythmias or ST-T changes on ECG were seen in any patient in either of the groups.

Table 1 The demographic profile in the two groups

	Group M (n-30)	Group D (n-30)	P Value
Age (years)	38.43 ± 9.84	38.6 ± 10.23	0.81
Gender (M:F) (n)	7:23	8:22	0.67
ASA I: II (n)	26:4	25:5	0.82

Table 2 Inter group comparison of heart rate between the two groups

	Heart rates ± SD (bpm)		P value
Time	**Group M**	**Group D**	
Baseline	77.66 ± 5.20	76.90 ± 4.75	0.6
5 min after start of trial drug infusion	76.23 ± 5.32	74.06 ± 5.52	0.57
10 min after start of trial drug infusion	74.86 ± 5.27	72.03 ± 5.16	0.039
At induction	75.36 ± 4.66	72.36 ± 4.64	0.015
At laryngoscopy and intubation	93.53 ± 6.83	80.00 ± 4.78	<0.0001
After laryngoscopy and intubation			
5 min	85.96 ± 4.62	78.83 ± 4.27	<0.0001
10 min	81.23 ± 4.46	76.83 ± 4.34	0.0003
20 min	80.83 ± 4.17	75.93 ± 3.92	<0.0001
30 min	81.03 ± 5.06	76.80 ± 3.29	0.0003
40 min	80.80 ± 4.26	77.40 ± 3.89	0.0021

Table 3 Inter group comparison of SBP between the two groups

	Systolic blood pressures (mmHg)		P value
Time	**Group M**	**Group D**	
Baseline	127.96 ± 6.23	126.26 ± 5.74	0.78
5 min after start of trial drug infusion	124.96 ± 5.82	120.73 ± 5.59	0.005
10 min after start of trial drug infusion	123.76 ± 5.66	119.26 ± 5.75	0.003
At induction	122.63 ± 5.83	118.56 ± 5.00	0.005
At laryngoscopy and intubation	157.46 ± 6.47	135.83 ± 5.52	< 0.0001
After laryngoscopy and intubation			
5 min	135.93 ± 5.48	128.96 ± 4.76	< 0.0001
10 min	131.8 ± 4.42	127.23 ± 4.68	0.0003
20 min	131.0 ± 4.26	126.40 ± 4.85	0.0003
30 min	130.93 ± 4.51	127.20 ± 5.39	0.005
40 min	131.36 ± 4.52	128.63 ± 4.71	0.025

Table 4 Inter group comparison of DBP (mmHg) between the two groups

	Diastolic Blood Pressures (mmHg)		P value
Time	**Group M**	**Group D**	
Baseline	77.33 ± 3.43	78.63 ± 4.16	0.69
5 min after start of trial drug infusion	75.66 ± 2.91	72.96 ± 4.52	0.008
10 min after start of trial drug infusion	74.63 ± 2.83	71.06 ± 4.23	0.0003
At induction	73.86 ± 3.61	70.33 ± 4.44	0.0013
At laryngoscopy and intubation	96.33 ± 5.80	85.90 ± 4.90	< 0.0001
After laryngoscopy and intubation			
5 min	85.90 ± 4.10	79.46 ± 4.49	< 0.0001
10 min	81.00 ± 3.37	78.86 ± 4.24	0.0352
20 min	80.90 ± 2.80	78.80 ±4.35	0.0304
30 min	81.46 ± 3.46	79.53 ± 3.73	0.0421
40 min	81.53 ± 3.59	79.23 ± 4.00	0.0228

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Table 5 Inter group comparison of MAP between the two groups

	Mean Arterial Blood Pressure (mmHg)		P value
Time	**Group M**	**Group D**	
Baseline	94.22 ± 3.25	94.20 ± 3.75	0.5
5 min after start of trial drug infusion	92.07 ± 2.86	88.88 ± 3.72	0.0005
10 min after start of trial drug infusion	91.00 ± 2.99	87.26 ± 3.54	< 0.0001
At induction	90.11 ± 3.53	86.40 ± 3.33	< 0.0001
At laryngoscopy and intubation	116.70 ± 4.59	102.54 ± 4.04	< 0.0001
After laryngoscopy and intubation			
5 min	102.57 ± 3.35	95.96 ± 4.08	< 0.0001
10 min	97.93 ± 2.61	94.98 ± 3.89	0.001
20 min	97.59 ± 2.33	94.66 ± 3.84	0.0007
30 min	97.95 ± 2.33	95.41 ± 3.41	0.001
40 min	98.14 ± 2.90	95.69 ± 2.96	0.002

Discussion

We observed from our study that administration of preanaesthetic single dose intravenous Dexmedetomidine in a dose of 0.06 mcg/kg body weight has better control of hemodynamic as compared to intravenous midazolam 0.05mg/kg body weight during induction and surgical intervention studied up to a time interval of 40 minutes after completion of the study drugs administration. Intravenous Dexmedetomidine has been used as premedication at different doses in the range of 0.5-1 mcg/kg body weight[5–10] The dose of 0.33 µg/kg to 0.67 µg/kg seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia.[11] Equipotent dose of Dexmedetomidine and midazolam has not been studied or reported. Midazolam has also been used in different doses as premedication in various studies ranging from 0.02-0.08mg/kg.[12–16] So in our study we used optimal doses of both the study drugs for obtundation of hemodynamic response.

We found that after administration of study drugs, there was fall of blood pressure and heart rate initially from the baseline values. The maximum fall in SBP, DBP and MAP was at induction of anesthesia. The fall was significantly more in group D as compared to group M ($p<0.05$). However this change was not clinically significant as percentage change was less than 10% of each parameter as compared from baseline values. This enhanced initial reduction in blood pressure and heart rate in Dexmedetomidine group could be due to central sympatholytic and also anxiolytic effect of Dexmedetomidine.[11] Mild reduction of blood pressure and heart rate in the midazolam group after drug administration could be due to sedative and anxiolytic property of midazolam, which brought back the raised haemodynamic parameters due to preoperative anxiety, towards normal. The initial reduction in blood pressure and heart rate in the Dexmedetomidine group in our study correlate well with previous studies.[5,6,12] Aantaa et al.[17] reported a statistically significant decrease in blood pressure and heart rate after administration 0.67 and 1 mcg/kg of Dexmedetomidine. The fall in blood pressure was more in this study as compared to our study. This could be due to difference in the rate of infusion of the trial drugs. They administered Dexmedetomidine over 60 seconds, but in our study Dexmedetomidine was infused more slowly over 10 minutes. In another study, authors, compared the effects of intramuscular dexmedetomidine 1.0 mcg/kg, with those of midazolam 0.08 mg/kg and found moderate reductions in arterial pressure (maximally by 20%) and heart rate (maximally by 15%). They found higher fall in heart rate and blood pressure probably due higher dose of dexmedetomidine. Eren et al.[12] compared dexmedetomidine 0.1 mcg/kg and midazolam 0.02, 0.04 and 0.06 mg/kg body weight. They reported statistically significant decrease in blood pressure and heart rate in dexmedetomidine group 10 minutes after drug infusion. In the midazolam group there was statistically significant decrease in heart rate at 10 minutes, in the 0.04 and 0.06mg/kg groups. Though not statistically significant, there was also decrease in mean arterial pressure. Isik et al.[14] compared dexmedetomidine 1 mcg/kg intravenous and 0.05 mg/kg intramuscular midazolam and found initial decrease in mean arterial blood pressure and heart rate after administration of the trial drugs, in both the dexmedetomidine group and midazolam, though the decrease was not statistically significant.

In the present study, the maximum increase in blood pressure (systolic, diastolic, mean) and heart rate occurred at laryngoscopy and intubation in both midazolam and dexmedetomidine group. The increase was significantly higher in the midazolam group than the dexmedetomidine group ($p<0.0001$). The increase in haemodynamic parameters in the dexmedetomidine group from baseline parameters was clinically insignificant. Thus a single dose of 0.6 mcg/kg body weight of dexmedetomidine given as infusion before induction of anesthesia obtunded the haemodynamic response to laryngoscopy and intubation more effectively in comparison to 0.05 mg/kg body weight of midazolam. In a study, authors also reported that 1 mcg/kg dexmedetomidine have similar increase in blood pressure and heart rate in response to tracheal intubation.[18] The maximum average increase in heart rate in their study was 7%, whereas in our study it was 4%. Slight difference in the values may be due to dose differences. Though the dose of dexmedetomidine in their study was more than our study, they used intravenous fentanyl 1 mcg/kg body weight, but in our study 1.5 mcg/kg fentanyl was used. However, they reported bradycardia in two cases in contrast to none in our study. Isik et al.[14] reported mean arterial pressure and heart rate in midazolam group (0.05 mg/kg) to be significantly higher than dexmedetomidine group (1 mcg/kg) after laryngoscopy and intubation ($P<0.001$). Basar et al.[10] used 0.5 mcg/kg dexmedetomidine and reported significant increase in heart rate and blood pressure after endotracheal intubation in the control group as compared to dexmedetomidine group.

The surgical stress response may cause hemodynamic perturbations and needs to be controlled. In the dexmedetomidine group, 5 minutes after laryngoscopy and intubation all the studied haemodynamic parameters returned to near baseline values ($p>0.05$). All the parameters remained comparable to the baseline values thereafter; throughout the intraoperative study period i.e. up to 40 min from laryngoscopy and intubation. However, in the midazolam group, all the haemodynamic parameters remained raised at 5 minutes in comparison to the baseline values ($P<0.05$) and remained so thereafter, throughout the

intraoperative study period. Also, inter group comparison shows that the studied haemodynamic parameters were consistently higher in the midazolam group than the dexmedetomidine group till the end of the study period ($p<0.05$). These results are similar to Erkola et al.,[15] Scheinin et al.[19] where they reported blood pressure and heart rate in midazolam group to be higher than the dexmedetomidine. However they used higher doses of dexmedetomidine and was associated with bradycardia and hypotension in contrast to none in our study. Basar et al.[10] also reported better intraoperative haemodynamic stability in the dexmedetomidine group (0.5mcg/kg) than the placebo group.

In our study after administration of the trial drugs, decrease in SpO_2 in the midazolam group was significantly more than that in the dexmedetomidine group ($p<0.05$). This decrease was clinical not significant as SpO_2 was always more than 95%. This finding in our study is supported by Eren et al.[12] who found significant decrease in SpO_2 in midazolam group (0.06 mg/kg) in comparison to dexmedetomidine group (1mcg/kg). This may probably due to the sedative effects of both the drugs, and greater fall in SpO_2 in the midazolam group was probably due to its respiratory depressant effect as well. However, fall in SpO_2 was not clinically significant in either group. Both the drugs were well tolerated and no serious haemodynamic was observed. Dryness of mouth which is a common side effect of dexmedetomidine was observed in 3 patients of dexmedetomidine group.

Our study may be limited by the fact that we studied these drugs only in ASA Physical status I and II and may not be applicable to other physical status patients. The patients with cardiovascular or diabetic disease may show different response to these drugs and also the hemodynamic response to perioperative stress. This needs further evaluation in this group of patients. Also cost benefit analysis was not estimated by us and needs further research. Hence we conclude that a single intravenous pre-anesthetic dose of dexmedetomidine of 0.6 mcg/kg body weight blunts haemodynamic response to laryngoscopy and intubation more efficiently and maintain the intraoperative haemodynamic stability in comparison to 0.05 mg/kg dose of midazolam. We recommend that dexmedetomidine may be used to blunt haemodynamic response to laryngoscopy and intubation.

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Conflicts of interest

Authors declare that there is no conflicts of interest.

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