ORIGINAL ARTICLE

Comparative Evaluation of Dexmedetomidine, Fentanyl, Magnesium Sulphate and Control Group to Attenuate Pressor Responses and Airway Reflexes to Intubation During General Anaesthesia

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Abstract

This study evaluated the efficacy and safety of dexmedetomidine, fentanyl and magnesium sulphate to find out safe anaesthetic technique so that pressor response changes and airway reflexes at the time of extubation are not harmful to the patient. This prospective, randomized study was conducted on 100 patients in the Government Medical College and Associated Hospitals, Jammu. The patients enrolled were those undergoing elective surgical procedures under endotracheal anaesthesia, of ASA Grade-I, within the age group of l8-65 years, of either sex. Pulse rate, blood pressure, electrocardiogram and oxygen saturation were recorded during preinduction, just before extubation, and l, 2, 3, 5 and 10 minutes after extubation. Mean arterial pressure at those intervals was calculated. Any laryngospasm, tracheal collapse, laryngeal edema, vocal cord paralysis, pulmonary edema and laryngeal incompetence bronchospasm, or desaturation was recorded. The time for requirement of first analgesic dose post-operatively was noted.The data so collected was analyzed, compared and subjected to statistical analysis. There was statistically significant rise in mean heart-rate 1 and 2 minutes after extubation in all the groups ($p<0.05$) except in dexmedetomidine group. Mean heart rate decreased to non-significant levels in magnesium sulphate and fentanyl groups at 3 minutes, whereas it remained significant in the control group upto 5 minutes. Before extubation and after extubation, mean SBP, mean DBP and mean ABP shot up significantly in the control group.Dexmedetomidine is more effective as compared to magnesium sulphate and fentanyl in attenuating the rise in heart rate and blood pressure after extubation. There are no adverse effects seen in patients treated with dexmedetomidine.

Keywords

Dexmedetomidine, Magnesium Sulphate, Fentanyl

Introduction

Balanced anaesthetic technique including use of induction agents, muscle relaxants and endotracheal intubation with minimal haemodynamic disturbance of the patients ensures success of all major and specialized surgical procedures. An essential component of general anaesthesia, endotracheal intubation serves in maintenance of the patency of upper airway, proper ventilation, reduction in the risk of aspiration and delivery of the inhalational anaesthetic agents to the patients through breathing circuits. There is marked sympathetic stimulation and increase in catecholamine concentration in susceptible individuals due to tracheal intubation (1).

Frequency and degree of hemodynamic changes are significant in patients who are susceptible to systemic hypertension, coronary artery disease, valvular heart disease, cerebrovascular disease and intracranial aneurysm. Herein these transient changes can result in potentially deleterious effects like acute left ventricular failure, arrhythmia, myocardial ischemia, rupture of cerebral aneurysm (2).

Tracheal extubation, translaryngeal removal of a tube from the trachea, can also be associated with detrimental airway and hemodynamic

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responses. Smooth extubation requires the absence of straining, movement, coughing, breath holding and laryngospasm. Many drugs are used to attenuate the intubation response such as intravenous lignocaine, short-acting opioids such as fentanyl and remifentanil, esmolol, labetalol, intratracheal local anesthetic instillation, dexmedetomidine which can be used during extubation also (3).

Adrenergic alpha 2 agonists seem to have the ability to attenuate the pressor response to intubation and extubation (4). Dexmedetomidine, a selective ?2 -agonist, has sedative, analgesic as well as sympatholytic properties. It has also been shown to be effective in maintaining hemodynamic stability during intubation and extubation without prolonging recovery. It also helps in attenuating airway reflex response to tracheal extubation. The unique property of dexmedetomidine is that it produces minimal respiratory depression and has been approved by FDA for ICU sedation less than 24 hours. Dexmedetomidine also reduces the requirements of other anaesthetic agents like volatile anaesthetics and thiopentone sodium (5).

Fentanyl, a synthetic opioid, has been reported to reduce the prevalence of coughing during and after extubation and to suppress the sneezing reflex after abdominal hysterectomy and periocular injections. Fentanyl has also been reported to attenuate the cardiovascular responses to tracheal extubation in elective gynecologic surgery (6).

Magnesium sulphate is widely used in order to decrease the hemodynamic response to airway management, with proven effectiveness. It blocks the release of catecholamines from adrenergic nerve terminals and adrenal gland, has cardioprotective and antiarrhythmic action, and induces coronary and systemic vasodilation by antagonizing calcium ion in vascular smooth muscle (7).

In the present study, efficacy and safety of dexmedetomidine, fentanyl and magnesium sulphate was evaluated to find out safe anaesthetic technique so that pressor response changes and airway reflexes at the time of extubation are abolished or they occur to the extent when they are not harmful to the patient.

Materials and Methods

This prospective, randomized study was conducted on 100 patients in the Department of Anaesthesia and Intensive Care, Government Medical College and Associated Hospitals, Jammu, after getting the approval from the Institutional Ethical Committee. The patients enrolled were those undergoing elective surgical procedures under endotracheal anaesthesia, of ASA Grade-I, within the age group of l8-65 years, of either sex. A pre-anaesthetic checkup was done one day prior to surgery which included detailed history, thorough clinical examination along with relevant investigations and weight of the patient.

Patients with history of COPD, emergency surgical procedures, pregnant women, morbid obese patients, patients with pharyngeal mass, preexisting cardiovascular disease and tose with significant respiratory, hepatic, renal, heamopoietic, endocrine dysfunction were excluded from the study. A written and informed consent was taken from all patients included in the study at the time of pre-anaesthetic evaluation.

Patients were prepared by overnight fasting. All the patients received 0.5 mg alprazolam orally night before surgery. Injection glcopyrolate 0.2 mg and injection voveron 75 mg i.m. was given 45 minutes prior to induction of anaesthesia. An intravenous line was secured in the preanaesthetic room. Injectioni pantoprazole 40 mg i.v. was administered 15 minutes before surgery. Patients were allocated to one of the following four study groups using the process of randomization with the help of computer or the table of random numbers. The procedure of randomization involved usage of serially numbered envelopes with the predetermined allocation as below.

Each group had 25 patients. Group A patients were given dexmedetomidine 0.5 microg/kg in 100 ml of isotonic saline five minutes before extubation, Group B patients were given magnesium sulphate 30 mg/kg in l00 ml of isotonic saline five minutes before extubation, Group C patients were given fentanyl 1 ?g/kg in 100 ml of isotonic saline five minutes before extubation and Group D patients were given 100 ml of isotonic saline five minutes before extubation.

After receiving patients in the operating room, monitors were attached to the patients and all parameters i.e. heart rate, blood pressure, oxygen saturation and electrocardiograph was noted. Then patients were given injection ondansterone 0.1 mg/kg and injection tramadol l mg/kg body weight. Patients were preoxygenated with 100% oxygen for 3 minutes. Intravenous induction was carried out with sleeping dose of injection thiopentone sodium (3-5mg/kg). After the loss of eyelash reflex, injection succinylcholine (l-l.5mg/kg) was administered. After one minute, patients were intubated with cuffed endotracheal tube of appropriate size and air entry was checked for proper placement of endotracheal tube and tube was secured in place.

Anaesthesia was maintained with oxygen (33%) ± nitrous oxide (67%) ± halothane and vecuronium bromide

0.l mg/kg. Intraoperative monitoring of heart rate, blood pressure, electrocardiogram, and oxygen saturation was done throughout the surgery. Five minute before extubation patient was given drug according to the group allocated to him/her. Inhalation agent and nitrous oxide were stopped when surgery was complete.

At the end of procedure patients were reversed with injection glycopyrrolate 0.0l mg/kg and neostigmine 0.05 mg/kg i.v. Oropharyngeal secretions were aspirated before extubation. The endotracheal tube was removed smoothly when patient was completely conscious and responded to verbal commands. Pulse rate, blood pressure, electrocardiogram and oxygen saturation were recorded for the study at the following intervals: preinduction, just before extubation, and l, 2, 3, 5 and 10 minutes after extubation. Mean arterial pressure at those intervals was calculated. Any laryngospasm, tracheal collapse, laryngeal edema, vocal cord paralysis, pulmonary edema and laryngeal incompetence bronchospasm, or desaturation was recorded. Any post-operative sedation seen was assessed by a five point sedation scoring given by Yeager in 1987: 0 - mildly conversant, 1 - mildly sedated, 2 - moderately sedated and drowsy, 3 - asleep but arousable, and 4 - asleep not arousable (8). The time for requirement of first analgesic dose post-operatively was noted.The data so collected was analyzed, compared and subjected to statistical analysis.The data was analyzed with the help of computer software MS Excel and SPSS for windows. Baseline comparability of the patients in all the four groups was ascertained by using Chi-square test/ANOVA as appropriate. Haemodynamic measurements at various intervals were expressed as mean and standard deviation. Change in the reflex response was expressed as percentage terms. ANOVA was used to evaluate inter-group difference in mean values followed by the use of Bonferroni 't' test. A p-value of less than 0.05 was considered as statistically significant .All p value reported were two tailed.

Results

In the study, there was no significant difference among the four groups with respect to mean age and mean weight (*Table 1*). There was statistically significant rise in mean heart-rate 1 and 2 minute after extubation in all the groups ($p<0.05$) except in dexmedetomidine group. Mean heart rate decreased to non-significant levels in magnesium sulphate and fentanyl groups at 3 minutes, whereas it remained significant in the control group upto 5 minutes (Table 2). Moreover, just before extubation and after extubation, mean systolic blood pressure, mean diastolic blood pressure and mean arterial blood pressure shot up significantly in the control group (*Tables 3, 4, 5*). Time for requirement of first analgesic is given in *Table 6*, while incidence of common side effects is given in *Table 7*.

Discussion

The present study was conducted to study the effects of dexmedetomidine 0.5 µg/kg, magnesium sulphate 30 mg/kg and fentanyl 1 µg/kg on attenuation of pressor response to tracheal extubation. A total of100 patients ASA Grade I of either sex between 18-65 years of age undergoing elective surgery were divided in four groups of 25 each. There was statistically no significant difference in mean values of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure amongst the four groups before intubation. The mean age and mean weight of the patients in all the four groups were statistically comparable. No case of laryngospasm, bronchospasm or desaturation was recorded. In the dexmedetomidine group, there was increase in heart rate from 85.47±9.94 to 91.80±8.15 and 88.80±6.33 bpm respectively, at preextubation and 1 min after extubation, which were statistically significant ($p<0.05$). Thereafter a decline in the heart rate was observed which was statistically not significant till 3 minutes. At 5 and 10 minutes, heart rate lowered to 72.83 bpm which was statistically significant when compared to preinduction value ($p<0.05$). There was increase in SBP in preextubation, 1, 2 and 3 minutes after extubation which was statistically significant at 1 minutes and non significant at 2, 3 and 5 minutes when compared to preinduction value. However, a decline in SBP was observed at 10 minutes which was statistically significant as compared to the basal value ($p<0.001$). Similar trends were observed with DBP and MAP also. When compared to the control group heart rate, SBP, DBP and MAP were lower in the dexmedetomidine group which was statistically significant ($p <0.001$) at various time intervals of our study, but no intervention was required as this fall in pulse rate was transient and did not affect

Table. 1 Demographic profile

Groups	Age (in years) Mean ± SD	Weight (in kgs) Mean ± SD
A (Dexmedetomidine)	37.36± 12.99	72.12±13.67
B (Magnesium sulphate)	40.64±12.62	70.84±12.53
C (Fentanyl)	40.52±10.82	74.20±15.95
D (Control)	35.80±13.47	71.76±17.58
Statistical inference (Anova test)	$p = 0.43^{**}$	$p = 0.88^{**}$ **Not significant

Table 2. Comparison of Mean Heart Rate Changes in the Four Groups Before and After Extubation

Time	Groups							
	A (Dexmedetomidine)		B (Magnesium sulphate)		C (Fentanyl)		D (Control)	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Pre Induction	85.47±9.94	0.001*	84.23±9.74	0.002*	84.23±7.39	0.005*	87.12±9.74	0.002*
Pre Extubation	91.80±8.15		92.27±7.33		93.60±22.64		95.76±14.87	
After Extubation								
1 Min	88.80±6.33	0.099	92.27±7.15	0.002*	90.76±11.4	0.002*	104.87±11.17	0.000*
2 Min	85.60±5.97	0.275	88.10±6.94	0.032*	89.20±13.17	0.035*	102.27±10.27	0.000*
3 Min	79.17±5.71	0.275	85.40±6.68	0.490	86.52±12.80	0.376	96.60±10.17	0.001*
5 Min	72.83±4.47	0.002*	81.13±6.23	0.066	82.24±12.28	0.451	92.20±9.70	0.026*
10 Min	72.83±6.31	0.000*	78.53±4.23	0.000*	78.28±9.51	0.004*	84.20±8.96	0.245

*Significant

Table 3. Comparison of Mean Systolic Blood Pressure Changes in the Four Groups Before and After Extubation

Time	Groups							
	A (Dexmedetomidine)		B (Magnesium sulphate)		C (Fentanyl)		D (Control)	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Pre Induction	120.28±10.68	0.001*	122.64±14.89	0.002*	128.60±12.95	0.005*	121.36±9.99	0.002*
Pre Extubation	135.54±9.20		132.96±13.20		135.32±13.29		142.00±22.55	
After Extubation								
1 Min	140.56±9.71	0.002*	141.56±11.37	0.099	141.96±7.60	0.099	163.92±6.52	0.000*
2 Min	132.36±7.39	0.321	139.08±11.72	0.275	138.76±8.72	0.375	162.44±6.21	0.000*
3 Min	125.92±5.99	0.491	136.36±12.42	0.275	136.80±7.90	0.378	157.84±7.18	0.001*
5 Min	117.76±6.82	0.067	133.20±11.51	0.062	132.80±8.27	0.451	153.16±8.37	0.027*
10 Min	111.64±9.61	0.000*	124.48±7.88	0.000*	127.88±5.76	0.906	147.12±21.32	0.251

*Significant

Table 4. Comparison of mean diastolic blood pressure changes in the four groups before and after extubation

Time	Groups							
	A (Dexmedetomidine)		B (Magnesium sulphate)		C (Fentanyl)		D (Control)	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Pre Induction	72.96±10.48	0.001*	75.72±11.37	0.002*	76.96±11.22	0.005*	69.80± 9.59	0.002*
Pre Extubation	75.36±9.31		70.36±12.09		75.80±11.70		79.44±21.15	
After Extubation								
1 Min	94.36±9.88	0.002*	92.92±10.78	0.099	95.36± 9.43	0.099	105.76±8.10	1.000
2 Min	86.16±8.01	0.321	90.40±10.82	0.271	92.28±9.44	0.365	104.52±7.10	0.000*
3 Min	80.48±7.84	0.470	87.88±10.94	0.276	89.68±9.34	0.375	102.12±7.15	0.001*
5 Min	88.64±6.13	0.066	99.08±8.76	0.012*	101.41±8.04	0.452	116.68±7.38	0.027*
10 Min	69.60±6.59	0.000*	76.52±5.72	0.000*	79.88±6.92	0.706	101.20±6.46	0.251

*Significant

Table 5. Comparison of mean arterial blood pressure changes in the four groups before and after extubation

	Groups							
Time	A (Dexmedetomidine)		B (Magnesium sulphate)		C (Fentanyl)		D (Control)	
	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value	Mean ± SD	p-value
Pre Induction	91.96±5.92	0.001*	93.32±8.22	0.002*	94.28±6.99	0.005*	95.20±5.59	0.002*
Pre Extubation	95.64±12.23		91.23±12.46		94.75±9.28		100.29±21.62	
After Extubation								
1 Min	109.80±9.33	0.002*	109.16±10.57	0.099	110.89±8.46	0.099	125.12±6.74	0.000*
2 Min	101.52±7.35	0.321	106.64±10.66	0.490	107.77±8.88	0.357	123.80±6.12	0.000*
3 Min	95.72±6.70	0.257	104.08±10.98	0.256	105.38±8.52	0.367	120.68±6.54	0.001*
5 Min	88.64±6.12	0.066	99.08±8.76	0.210	101.41±8.04	0.542	116.68±7.38	0.027*
10 Min	83.64±6.00	0.000*	92.56±6.00	0.000*	95.88±6.32	0.911	108.16±8.96	0.254

*Significant

Table 6. Time for requirement for first analgesic in the four groups

Patient No.	Groups			
	A	B	C	D
	(Dexmedetomidine)	(Magnesium sulphate)	(Fentanyl)	(Control)
1	180 min	60 min	60 min	30 min
2	150 min	60 min	50 min	25 min
3	180 min	45 min	60 min	35 min
4	180 min	45 min	50 min	35 min
5	120 min	45 min	55 min	35 min
6	150 min	60 min	55 min	35 min
7	180 min	60 min	60 min	25 min
8	180 min	60 min	60 min	25 min
9	180 min	75 min	55 min	30 min
10	120 min	45 min	45 min	30 min
11	120 min	60 min	40 min	25 min
12	150 min	75 min	45 min	25 min
13	150 min	30 min	45 min	35 min
14	120 min	35 min	45 min	40 min
15	150 min	30 min	50 min	40 min
16	180 min	35 min	40 min	35 min
17	180 min	35 min	50 min	35 min
18	120 min	35 min	45 min	30 min
19	120 min	35 min	50 min	30 min
20	150 min	30 min	60 min	35 min
21	180 min	30 min	40 min	35 min
22	210 min	30 min	50 min	35 min
23	210 min	35 min	60 min	35 min
24	180 min	35 min	60 min	35 min
25	120 min	35 min	60 min	30 min
Mean	**158.4 min**	**44.8 min**	**51.6 min**	**32.2 min**

Table 7. Incidence of common side effects in the four groups

Side effects	Groups			
	A (Dexmedetomidine) No.	B (Magnesium sulphate) No.	C (Fentanyl) No.	D (Control) No.
Apnea	0	2	5	2
Gagging or coughing	0	0	0	10
Laryngospasm	0	0	0	0
Bronchospasm	0	0	0	0
Tracheal collapse	0	0	0	0
Vocal cord palsy	0	0	0	0
Pulmonary edema	0	0	0	0

the blood pressure. The sedation score in all the patients of dexmedetomidine group remained 0 (mildly conversant) signifying no sedation in the post extubation period in the patients receiving dexmedetomidine.

Our observations are in accordance with the findings of Recep et al. who reported that dexmedetomidine was not associated with increased HR and SBP after extubation compared with the preextubation values and that none of the patients were sedated after receiving 0.5 ?g/kg of dexmedetomidine bolus dose (9). Guller et al. also reported that dexmedetomidine was associated with less significant increase in HR, SBP and DBP at extubation. The mechanism by which dexmedetomidine acts is due to reduction of intracellular cyclic adenosine monophosphate (c-AMP) and c-AMPdependent protein kinase activity, resulting in dephosphorylation of ion channels (10). It also reduces the norepinephrine turnover and decreasing central sympatholytic outflow, resulting in decreased heart rate and blood pressure. Recovering from anaesthesia often results in elevating catecholamine concentration following withdrawal of anaesthetics at the culmination of surgery. This response is further aggravated by the laryngeal manipulations occurring at the time of extubation. Dexmedetmidine reduces heart rate and blood pressure (11) and the hemodynamic and catecholamine responses to intubation and extubation (10). Dexmedetomidine induces sedation and analgesia without affecting respiratory status. It also reduces the prevalence of emergence agitation (12). In our study we made use of these properties of dexmedetomidine for providing a smooth transition from the pre-extubation to the post-extubation phase by minimizing the haemodynamic fluctuations.

In the magnesium sulphate group, heart rate increased from 84.23±9.74 to 92.27±7.33 at the preextubation which was statistically significant ($p < 0.05$). The heart rate remained increased than the basal values but was statistically not significant at 3 and 5 minutes after extubation. A statistically significant rise in SBP was observed at preextubation ($p < 0.001$) in the magnesium group. The increase in the SBP persisted for1, 2 and 3 minutes after extubation but the difference in SBP was statistically insignificant compared to the baseline value ($p > 0.05$). Similar findings were seen with DBP and MAP also. Though there was increase in SBP, DBP and MAP, it was of smaller magnitude and of lesser duration in the magnesium treated group as compared to the control group. Seventeen of the patients in the magnesium sulphate group had sedation score of 2 (moderately sedated and drowsy) and rest 8 had sedation score of 3 (asleep but arousable). These differences were statistically significant as compared to the control group and the dexmedetomidine group but were clinically insignificant. Our study is in accordance to Arar et al. (13). Magnesium sulphate inhibits the hemodynamic responses to intubation, as it inhibits catecholamine release from adrenergic nerve endings (14). It also reduces the hemodynamic responses to extubation. Its perioperative administration can reduce perioperative pain and requirement of analgesic agent (13).

In the fentanyl group, heart rate increased from 84.23±7.39 to 93.60±22.64 bpm in the preextubation group. The heart rate remained increased than the basal values but was statistically not significant at 3 and 5 minutes after extubation. A statistically significant rise in SBP was observed at preextubation ($p<0.001$).

In the magnesium group, the increase in the SBP persisted for 1, 2, 3 and 5 after extubation but the difference in SBP was statistically not significant compared to the baseline value ($p>0.05$). Similar findings were seen with DBP and MAP also. Though there was increase in SBP, DBP and MAP, it was of smaller magnitude and of lesser duration in the fentanyl treated group as compared to the control group.

Five patients in the fentanyl group had sedation score of 1 (mildly sedated) and rest 20 had sedation score of 2. These differences were statistically significant in comparison to dexmedetomidine and control but clinically insignificant. Our study is in accordance to Recep et al. (9). Fentanyl causes significant attenuation of the pressor response to laryngoscopy and intubation. Fentanyl diminishes the increase in plasma catecholamine concentrations elicited by tracheal intubation and surgical stress.

In the dexmedetomidine group, bradycardia (HR <45 beats/minute) and emesis was not observed in any patient. In the fentanyl group, bradycardia was not observed in any patients, vomiting in 1 patient, and shivering in 1 patient. There were no significant differences in the prevalence ($p>0.05$) of adverse events (e.g. breath holding or desaturation) between the three groups. HR, SAP and DAP increased at extubation in all the groups ($p<0.05$), but the increase was less significant with dexmedetomidine. The time from tracheal extubation and emergence from anaesthesia were similar in all the groups. Postoperative somnolence and respiratory depression were not observed in any patients in any of the study groups.

Conclusion

The study concludes that dexmedetomidine, magnesium sulphate and fentanyl are effective in attenuation of pressor response to extubation. However, dexmedetomidine is more effective in attenuating the rise in heart rate and blood pressure after extubation and is associated with better extubation quality as depicted by lower sedation scores and no adverse effects seen in patients treated with dexmedetomidine.

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