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A comparative study between dexmedetomidine, clonidine and magnesium sulfate in attenuating hemodynamic response to laryngoscopy and intubation – a randomised study

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Abstract

Introduction: The stress responses to laryngoscopy comprising of elevation in heart rate and rise in systolic and diastolic pressure are well known. The potential for life threatening complications associated with these responses is also well documented. Therefore, it has become very much necessary to discover a drug which can abolish this response. The present study is designed to study the effectiveness of dexmedetomidine (D), clonidine (C) and magnesium sulfate (M) in attenuating the hemodynamic response to laryngoscopy in patients undergoing surgeries.

Methods: This study was carried out on 120 ASA grade I & II patients aged 18 to 55 years scheduled for elective surgical procedures under general anesthesia lasting for more than 2 hours. Patients were divided randomly into 3 groups, group D received 1mcg/kg of dexmedetomidine, group C received 1 mcg/kg of clonidine and group M received 30 mg/kg of magnesium sulfate. Data were entered in excel sheet and analysed by SPSS software. Qualitative data were expressed by number and percentage. Quantitative data were presented by mean +/- SD.

Results: Comparison of three groups reveals that hemodynamic variables were similar within the groups at baseline and at 5min before intubation while there were significant difference between them starting from just after the intubation, 30 sec after intubation then 1 min, 2min, 3min, 4min, 5 min, 10min after intubation.

Conclusions: Dexmedetomidine (1mcg/kg) in comparison to magnesium sulfate (30mg/kg) and clonidine (1 mcg/kg) is far more effective in blunting the hemodynamic response to laryngoscopy.

Keywords: Dexmedetomidine, Magnesium sulfate, Clonidine, Intubation, Hemodynamic response, Laryngoscopy, General anaesthesia

Introduction

Success of all major and specialized surgical procedures depends on balanced anaesthetic techniques, with use of induction agents, muscle relaxants and endotracheal intubation with minimal haemodynamic disturbance to the patients. Endotracheal intubation is an essential component of general anaesthesia as it serves many purposes including maintenance of the patency of upper airway, proper ventilation, reduction of the risk of aspiration and delivery of the inhalational anaesthetic agents from anaesthesia machine to the patients through breathing circuits. Laryngoscopy and tracheal intubation are noxious stimuli resulting in marked sympathetic stimulation and increased catecholamine concentration in susceptible individuals.(1,2) Frequency and degree of hemodynamic changes are significant in susceptible patients, particularly those with systemic hypertension, coronary artery disease, valvular heart disease, cerebrovascular disease, and intracranial aneurysm, where even these transient changes can result in potentially deleterious effects e.g. acute left ventricular failure, arrhythmia, myocardial ischemia, rupture of cerebral aneurysm.(3,4) Traditionally used drugs like lignocaine, fentanyl, esmolol etc. are either not fully effective or may results in considerable adverse effects.

The present study was designed to study the effectiveness of Dexmedetomidine, Clonidine and magnesium sulfate in attenuating hemodynamic response to laryngoscopy in patients who undergoes surgeries under general anesthesia and at the same time to note any adverse effect of both the drugs during intraoperative and postoperative period.

Materials and Methodology

The study was conducted after taking due ethical permission and consent in written format from all the patients. This prospective randomized single blinded study was carried out on 120 ASA grade 1 & 2 patients aged 18 to 55 years scheduled for elective surgical procedures under general anesthesia lasting for more than 2 hours. Patients were divided randomly into 3 groups of 40 each. Group D received inj. Dexmedetomidine 1 mcg/kg, group C received inj Clonidine 1 mcg/kg and group M received inj. magnesium sulfate 30 mg/kg.

All patients were examined on the day before surgery and Informed consent were taken from each patient. Routine investigations like Hb, TLC, DLC, LFT, RFT, ECG, X-Ray chest (PA view), Fasting/ Random Blood Sugar, Platelet count were done. Patients with ASA grade I and II, within age group of 18 to 55 years with body weight between 30 to 70 kg were included in the study. Patients with major organ dysfunction (ASA grade III, IV, V) or any major medical illness e.g.

Pulmonary koch's, Diabetes, Hypertension, Thyroid disorder etc., on medications like hypnotics, narcotic, alpha2 agonists, CCB, beta blocker etc., with predicted difficult intubation and having known allergy to anesthetic agents used in the study were excluded from the study.

On arrival in the operation theatre, patient's body weight, fasting status, consent and preoperative evaluation (done previously) were checked. Baseline parameters SpO2, Pulse rate (PR), Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) were recorded. Mean arterial blood pressure (MBP) was calculated by formula - DBP+ Pulse pressure/3. Two IV lines with 18/20 G cannula were secured. Ringer lactate drip was started through one IV cannula.

All the patients were premedicated with injection fentanyl (1µg/kg) and injection midazolam (0.03mg/kg) intravenously.

Test drug infusion (dexmedetomidine/ clonidine/ magnesium sulfate) was commenced in a single blind fashion. Infusion was prepared by mixing 1 µg per kg of dexmedetomidine (group D)/ 1 µg per kg of clonidine (group C)/ 30 mg per kg of magnesium sulfate (group M) in 100 ml of normal saline. The total drug was infused in 10 min. The infusion was continued for 10 min. PR, SBP, DBP and SpO2 were recorded after stabilization period of 5 min. The hemodynamic measurements were repeated at the end of infusion i.e. at 10 min. The patients were pre oxygenated with 100% O_2 at 8 lit/min for 3 min during this period**.** At the end of infusion, induction of anesthesia was done with inj. Thiopentone sodium at a dose sufficient to abolish eyelash reflex, followed by inj. Vecuronium 0.12 mg/kg after recording hemodynamic measurements. Patient was ventilated with 100% oxygen for 3 mins. Hemodynamic measurements were recorded just before intubation. Intubation was done with cuffed portex endotracheal tube of appropriate size after direct laryngoscopy. Hemodynamic measurements were recorded 30 sec after intubation then 1 min, 2min, 3min, 4min, 5 min and 10min after intubation. Maintenance was done with 50% O_2 + 50% N_2O + Isoflurane. Muscle relaxation was provided by subsequent doses of inj. vecuronium (0.01 mg/kg). Reversal was done with inj. Neostigmine (0.05 mg/kg b. w.) and inj. glycopyrrolate (0.01mg/kg b. w.) after onset of spontaneous respiration. Any prevalence of laryngospasm, bronchospasm, desaturation or any intraoperative complications were recorded and managed according to standard protocols. Patients was shifted to recovery room and any immediate postoperative complication were recorded.

Statistical analysis: The sample size was calculated by taking the help of statistician and considering results of initial pilot study on 15 patients, with a goal of meaningful decrease in heart rate and MBP of 15 to 20% with estimated SD of 15 for HR and 20 for MAP, ensuring a power of 0.90 with alpha error of 0.05. This results in sample size of 35–38 patients in each group but expecting a 5% dropout rate, total 120 patients were considered in the study. The patients were randomized into three groups of 40 each, using random number table. Treatment was randomly allocated to the patients. Data were entered in excel sheet and analysed by SPSS software. Qualitative data were expressed by number and percentage. To observe the difference between the proportion, Chi square test or Fishers Exact test was used. Quantitative data were presented by mean +/-SD. Difference between the means were analysed by repeated ANOVA followed by Post Hoc test. Confidence interval were calculated and P value <0.05 was considered as significant level**.**

Results

There was no notable difference between the groups with respect to age, weight, surgical duration, ASA grading and type of surgery.

Table 1: Demographic characteristics and duration of surgery

Variables	Group D	Group M	Group C	P value between D&M	P value between C&M	P value between C&D
Age (in years) mean ± SD	33.00 ±9.47	35.15 ±13.03	32.60 ±12.32	0.4012	0.8711	0.3712
Weight (in kg) mean ± SD	53.00 ± 7.61	51.05 ± 5.23	51.00 ±5.40	0.1856	0.9666	0.1791
Duration of surgery (in min) mean ± SD	168.87 ± 26.98	173.62 ± 67.71	171 ± 50.01	0.6813	0.8444	0.8132

SD- Standard Deviation, D- Dexmedetomidine, M- Magnesium sulfate, C- Clonidine

Pulse Rate: Comparing the three groups, we observed that there was notable changes in heart rate between three groups except at baseline and at 5 min before intubation when the values were comparable. Although there is decrease in pulse rate in dexmedetomidine group, significant bradycardia not responding to treatment, was not noted in any of the cases.

Table 2: Comparison of mean change in pulse rate ± S.D. (from the baseline)

HR	D		C		M		P value [between group D & M]	P value [between group C & M]	P value [between group C & D]
	Mean	± SD	Mean	±SD	Mean	± SD			
Basal	86.5	14.2	87.6	9.3	85.7	6.8	.413	.510	.821
5Mins	84.1	13.8	86.7	8.6	87.4	9.4	.171	.246	.117
10Mins	77.6	13.0	92.4	8.2	90.2	9.6	.000	.451	.001
At Induction	73.8	11.7	90.4	8.5	92.6	10.3	.000	.456	.000
At Intubation	73.9	10.3	90.4	9.6	95.7	12.5	.000	.143	.000
30Sec	85.2	8.4	128.3	4.9	108.7	9.7	.000	.000	.000
1Min	82.5	8.9	125.1	6.6	105.2	10.1	.000	.000	.000
2Mins	80.8	8.3	116.8	8.2	101.6	9.2	.000	.000	.000
3Mins	76.4	9.1	110.7	8.0	99.0	7.3	.000	.000	.000
4Mins	75.4	8.4	99.7	8.5	96.4	6.5	.000	.174	.000
5Mins	72.0	7.5	98.9	6.6	94.6	7.7	.000	.063	.000
10Mins	72.6	7.0	99.1	7.1	93.6	7.4	.000	.022	.000

SD- Standard Deviation, D- Dexmedetomidine, M- Magnesium sulfate, C- Clonidine,

Systolic Blood Pressure: Comparing the mean SBP between all groups, we observed that there was notable difference between the groups just after laryngoscopy and at 30 sec, 1min, 2min, 3 min, 4min after laryngoscopy while the values were similar at baseline**.**

Table 3: Comparison of Mean ± S.D. of SBP (Systolic Blood Pressure)

SBP	D		C		M		P value [between group D & M]	P value [between group C & M]	P value [between group C & D]
	Mean	± SD	Mean	± SD	Mean	± SD			
Basal	127.8	12.2	128.7	6.6	128.1	8.5	.898	.953	.682
5Mins	128.4	14.1	128.0	4.5	129.9	8.4	.565	.211	.865
10Mins	122.9	12.3	126.3	5.5	124.1	7.6	.599	.142	.112
At Induction	112.4	11.6	127.9	4.6	122.4	6.3	.000	.003	.002
At Intubation	110.2	7.4	130.3	5.7	122.3	8.2	.000	.001	.000
30Sec	116.5	7.3	161.5	10.7	134.0	8.9	.000	.000	.000
1Min	113.6	8.3	158.5	3.8	130.4	8.0	.000	.000	.000
2Mins	105.9	10.7	148.6	8.2	127.1	7.2	.000	.000	.000
3Mins	103.2	10.6	137.9	8.3	123.7	7.9	.000	.000	.000
4Mins	100.9	8.7	128.0	5.8	119.8	6.2	.000	.000	.000
5Mins	98.9	7.5	132.1	6.0	121.5	6.0	.000	.000	.000
10Mins	99.0	6.2	128.8	4.8	121.7	6.9	.000	.001	.000

SD- Standard Deviation, D- Dexmedetomidine, M- Magnesium Sulfate, C- Clonidine

Diastolic Blood Pressure: When we compared the mean DBP between the three groups, we found that there was significant difference between the three groups just after intubation and at 30 sec, 1 min, 2 min, 3min after laryngoscopy. The mean changes in diastolic blood pressure were significantly different between the groups at all points of study except just before intubation when they were comparable.

Table 4: Comparison of Mean ± S.D. of DBP (Diastolic Blood Pressure)

DBP	D		C		M		P value [between group D & M]	P value [between group C & M]	P value [between group C & D]
	Mean± SD		Mean± SD		Mean± SD				
Basal	75.40	5.661	76.70	5.930	74.65	6.564	.483	.307	.701
5Mins	76.70	6.267	76.95	6.022	76.30	6.250	.898	.740	.841
10Mins	74.00	6.859	75.55	6.871	76.95	9.162	.107	.588	.315
At Induction	66.85	6.409	77.20	5.979	77.50	6.549	.000	.881	.000
At Intubation	72.95	7.783	77.90	7.130	76.35	4.913	.043	.428	.107
30Sec	80.55	7.458	106.20	4.549	85.55	5.960	.000	.000	.025
1Min	78.20	10.247	100.00	4.588	84.35	7.548	.000	.000	.037
2Mins	74.20	7.641	93.15	8.152	81.45	6.329	.000	.000	.002
3Mins	68.55	6.143	87.55	7.294	77.70	5.611	.000	.000	.000
4Mins	71.10	7.913	77.65	7.527	78.70	6.408	.011	.637	.002
5Mins	72.30	6.997	83.45	8.438	81.75	6.496	.000	.480	.000
10Mins	69.50	6.637	78.10	6.640	77.45	6.236	.000	.751	.000

SD- Standard Deviation, D- Dexmedetomidine, M- Magnesium sulfate, C- Clonidine

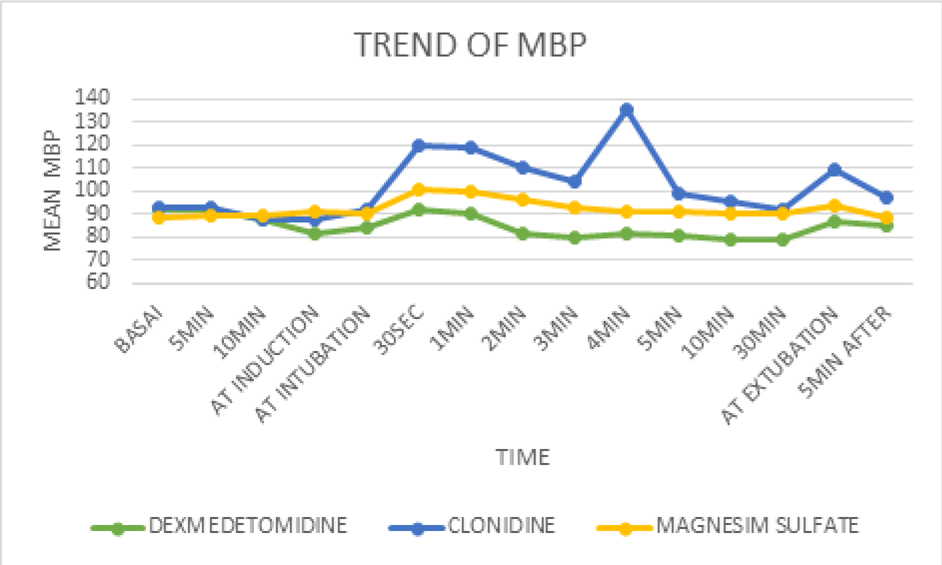

Fig. 1: Graph showing trend of mean blood pressure changes in all three groups

Mean Blood Pressure: Comparison of all groups reveals that MBP was similar in all three groups at baseline, 5min and at end of infusion (The similar trends were noted with SBP and DBP) while there were significant changes between the groups just after laryngoscopy, 30 sec, 1min, 2 min, 3min, 4min, 5min, 10 min after intubation (similar to trends of SBP and DBP). This further emphasizes the impact of Dexmedetomidine in stabilizing the hemodynamics of patient during and after laryngoscopy and intubation.

Table 5: Comparison of Mean ± S.D. of MBP (Mean Blood Pressure)

MBP	D		C		M		P value [between group D & M]	P value [between group C & M]	P value [between group C & D]
	Mean	± SD	Mean	± SD	Mean	± SD			
Basal	92.86	3.517	94.03	3.865	92.47	4.815	.471	.114	.167
5Mins	93.93	3.915	93.97	4.287	94.17	5.010	.812	.848	.965
10Mins	90.3	4.084	92.47	8.847	92.67	6.331	.0501	.908	.163
At Induction	81.55	5.652	87.70	8.979	91.10	4.962	.173	.043	.000
At Intubation	83.70	4.769	92.10	3.782	90.10	5.590	.000	.193	.000
30Sec	92.15	5.224	120.05	3.426	100.45	5.155	.000	.000	.000
1Min	90.05	6.186	119.40	3.362	99.65	7.680	.000	.000	.000
2Mins	81.40	6.739	110.55	7.280	96.40	7.863	.000	.000	.000
3Mins	79.55	4.872	104.10	6.561	92.90	6.423	.000	.000	.000
4Mins	81.05	7.783	105.30	5.250	91.20	5.970	.199	.294	.000
5Mins	80.45	5.286	98.80	8.244	90.85	5.224	.000	.001	.000
10Mins	78.65	6.467	95.60	4.695	90.25	5.210	.000	.002	.000

SD- Standard Deviation, D- Dexmedetomidine, M- Magnesium sulfate, C- Clonidine

There was no episode of significant hypotension or bradycardia during our study in all three groups. No patients were complaining about nausea, vomiting, difficulty in breathing postoperatively. There was no incidence of excessive sedation in any of the groups.

Discussion

The hemodynamic responses to laryngoscopy and intubation, comprising of elevation in heart rate and rise in systolic and diastolic pressure are well known. Till date lots of studies has been done to find the ideal drug which can suppress the response to laryngoscopy, at the same time without any undesirable side effects.

Dexmedetomidine is a newer α_2-agonist that received FDA approval in 1999. It is more selective α_2 -agonist than clonidine. It 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 so FDA has approve it for ICU sedation for less than 24 hours. Dexmedetomidine also reduces the requirements of other anaesthetic agents like volatile anaesthetics and thiopentone sodium.(5)

Clonidine is also a α_2-agonis with analgesic, sedative and anxiolysis properties. It acts on medullary vasomotor centre and stimulate alpha2 mediated inhibitory neurons resulting in decreases sympathetic outflow to peripheral vasculature. Like dexmedetomidine clonidine too helpful in maintaining hemodynamic stability during laryngoscopy and tracheal intubation, decreasing anaesthetic requirement during intraoperative period and providing additional analgesia.

Magnesium sulfate is a cerebral depressant which act by blocking NMDA receptor in CNS and by decreasing sympathetic outflow it decreases release of catecholamines resulting in vasodilator which primarily dilate arteries than veins. It has a calcium antagonist properties by competing with Ca for different channels in membrane and so can modify Ca mediated responses. Because of its NMDA receptor blocking action magnesium has been widely used for acute, chronic and postoperative pain management not as primary but as secondary analgesic. Because magnesium can decreases release of catecholamine from adrenal medulla and adrenergic nerves it can be safely use to suppress the effect of laryngoscopy and to provide cardiovascular stability.(6)

The present study was designed to study the effectiveness of dexmedetomidine (D), clonidine (C) and magnesium sulfate (M) in attenuating the hemodynamic response to laryngoscopy in patients undergoing surgeries under general anaesthesia.

We were using magnesium sulfate at a dose of 30 mg/kg according to study done by Panda et al who demonstrate that dose of 40mg/kg and 50mg/kg may lead to untoward side effect like hypotension.(7) Clonidine was used at a dose of 1 mcg/kg as Arora et al demonstrate that at a dose of 2 mcg/kg there was a significantly higher incidence of hypotension and postoperative sedation.(8) Rajan et al use clonidine at a dose of 1mcg/kg to measure the intraocular pressure changes after laryngoscopy and concluded that at this dose it can prevent the hemodynamic changes during laryngoscopy but unable to prevent rise in intraocular pressure.(9)

Just 30 sec after intubation in group D, the mean PR and DBP remained similar to preoperative value and SBP and MBP were decreased in relation to preoperative value. In group M there was slight increase in pulse rate, SBP, DBP and MBP as compared to baseline as well as when compared to values just before intubation. In group C, there was significant rise in pulse rate, SBP, DBP and MBP as compared to baseline as well as when compared to values just before intubation. When the three groups were compared there were notable changes in pulse rate, SBP, MBP and DBP between all groups.

One minute after intubation in group D, the mean PR and DBP, MBP remained similar to baseline and SBP decreased as compared to baseline. In group M there was slight increase in pulse rate, SBP, DBP and MBP as compared to baseline as well as when compared to values just before intubation. In group C, significant increase in pulse rate, SBP, MBP and DBP were noted.

At 2 min after intubation, in group D, the mean pulse rate and DBP again remain similar to baseline but SBP, and MBP decreased as compared to baseline while in group M, there was slight increase in pulse rate, SBP, DBP and MBP as compared to baseline as well as when compared to values just before intubation. In group C, significant increase in pulse rate, DBP, SBP and MBP compare to baseline.

3 minutes after intubation, in group D, the mean pulse rate, systolic, diastolic and mean blood pressure decreased as compared to baseline while in group M, the pulse rate was slightly increased as compared to baseline while SBP, DBP and MBP remained comparable to baseline,. In group C, significant increase in pulse rate, SBP, DBP, and MBP compare to baseline. Intergroup comparisons revealed significant difference in all the above mentioned variables at this point.

4 minutes after intubation, in group D, the mean pulse rate, systolic, diastolic and mean blood pressure remain decreased compared to baseline. In group M, the pulse rate was slightly increased as compared to baseline while systolic blood pressure, diastolic and mean blood pressure remained comparable to baseline. In group C, significant increase in pulse rate, DBP and MBP compare to baseline but SBP was comparable to baseline. This may be indicating that the effect of hemodynamic response to laryngoscopy and intubation has subsided in group C also. The mean change as compared to baseline, in all the variables mentioned above, was still significantly different in all groups. Thus dexmedetomidine has a significant effect on hemodynamic variables of patients and is highly effective in attenuating the changes in heart rate and blood pressure caused by laryngoscopy and intubation over and above clonidine and magnesium sulfate.

All the above mentioned facts suggest that dexmedetomidine (1mcg/kg) in comparison to clonidine (1mcg/kg) and magnesium sulfate (30mg/kg) was far more effective in stabilizing the hemodynamics of patients during and after laryngoscopy and intubation. We were using clonidine at a dose of 1mcg/kg as Arora et al and Rajan at al concluded that at this dose clonidine can effectively suppress the laryngoscopy response which was the ultimate goal of the present study.[8,9] They demonstrate that at a dose of 2 mcg/kg there was higher incidence of hypotension and sedation with clonidine which was highly undesirable in our study. But Tripathi et al demonstrate that clonidine 1 mcg/kg is ineffective in preventing hemodynamics changes during laryngoscopy in patient posted for laparoscopic cholecystectomy in comparison to clonidine 2mcg/kg.[10] Kalra et al found that clonidine 1.5 mcg/kg is far better than clonidine 1 mcg/kg and magnesium sulfate 50mg/kg in suppressing hemodynamic changes during pneumoperitoneum in laparoscopic cholecystectomy.[11] Puri et al shows that magnesium sulfate at a dose of 50mg/kg is effective in suppressing hemodynamic parameters during laryngoscopy in coronary artery disease patients.[12] So we may conclude that neither clonidine 1mcg/kg nor magnesium sulfate 30 mg/kg was effective in suppressing laryngoscopy responses in our study. But dexmedetomidine 1mcg/kg provided hemodynamic stability without significant increase in incidence of side effects.

Limitations

In this study hemodynamic changes were recorded only during induction and intubation and up to 10 mins thereafter. But effect of dexmedetomidine, clonidine and magnesium sulfate on hemodynamic parameters during intraoperative and postoperative period were not included in the present study.

Conclusions

Dexmedetomidine (1mcg/kg) in comparison to clonidine (1mcg/kg) and magnesium sulfate (30mg/kg) was far more effective in blunting the hemodynamic response to laryngoscopy in patients undergoing surgical procedures under general anesthesia.

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