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Anesthesiology

"STUDY OF INTRAVENOUSLY ADMINISTERED DEXMEDETOMIDINE ON ISOFLURANE REQUIREMENT AND PERIOPERATIVE HAEMODYNAMIC STABILITY IN ELECTIVE SURGERY"

Dr. Pauravi Bhatt	Associate Professor, Department of Anesthesiology, Smt. NHL Municipal Medical College & V.S. Hospital, Ahmedabad
Dr. Priyen Patel	3rd Year Resident, Department of Anesthesiology, Smt. NHL Municipal Medical College & V.S. Hospital, Ahmedabad
Dr. Devanshi Shah	3rd Year Resident, Department of Anesthesiology, Smt. NHL Municipal Medical College & V.S. Hospital, Ahmedabad
Dr. Nupur Doshi	2nd Year Resident, Department of Anesthesiology, Smt. NHL Municipal Medical College & V.S. Hospital, Ahmedabad

ABSTRACT

BACKGROUND : Dexmedetomidine is an α-2 adrenoreceptor agonist. The purpose of this study was to evaluate the effect of intravenous dose of dexmedetomidine on cardiovascular response resulting from laryngoscopy and endotracheal intubation, need for anaesthetic agent and perioperative haemodynamic stability

METHOD: Sixty patients scheduled for elective surgery were randomised into two groups (dexmedetomidine group and placebo group, n = 30 in each group). Fentanyl 1µg/kg was administered to all patients as premedication. Anaesthesia induction was done with Thiopentone sodium and succinycholine and anaesthesia was maintained with 33% oxygen :66% nitrous oxide, Vecuronium and Isoflurane. Isoflurane concentration was adjusted to maintain systolic blood pressure and/or heart rate within 20% of preoperative values. Haemodynamic parameters were recorded after intubation, 5minutes,10minutes ,30minutes,60minutes,90minutes and 120 minutes, after infusion stopped, after reversal and extubation. After extubation, All the patients in both the groups were monitored for VAS and sedation for at least 4 hours after surgery. Post-operative pain intensity was assessed using VAS score

RESULTS: After intubation and laryngoscopy there was an increase in pulse and blood pressure in both the group from baseline values. Maximum increase in pulse rate and blood pressure occur at intubation in both groups. But this increase statically significant in saline group patients. Mean Isoflurane concentration over intraoperative period is significantly less in Dexmetodomidine group as compared to saline group. Fentanyl requirement during the operation was reduced in the dexmedetomidine group . During postoperative period Ramsay sedation score is more in Dexmetodomidine group patients in comparison to saline group, but this difference is not statically significant.

CONCLUSION: Dexmedetomidine, as an adjuvant in general anaesthesia for elective surgeries provided a stable haemodynamic profile in perioperative period and effectively blunted pressor response to intubation and extubation, leading to minimal requirements for additional analgesics and potent inhalational agents. There was also an acceptable recovery profile.

KEYWORDS : Dexmedetomidine, Isoflurane,VAS score, Ramsay sedation score,

INTRODUCTION:

In general anaesthesia laryngoscopy, intubation and extubation are noxious stimuli and associated with stress responses and haemody namic changes in the form of laryngo-sympathetic stimulus which is manifested as hypertension, tachycardia and arrhythmias. These haemodynamic responses are well tolerated in otherwise healthy individuals but in patients with hypertension, coronary heart disease, cerebrovascular disease etc these transient changes can result in potentially deleterious effects.To prevent and counteract these effects an ideal agent required which should be safe, titrable, and rapidly acting has both sedative and analgesic properties with less side effects. Clonidine, α2 agonist, has been introduced to clinical anaesthesia for its sympatholytic, sedative, anaesthetic sparing effects and haemodynamic stabilising properties. Dexmedetomidine, the pharma cologically active d-isomer of medetomidine (4,[5]-[1-(2,3-dimethylphenyl)-ethyl] imidazole is a highly specific and selective α2 adrenoreceptor agonist. The α2:α1 binding selectivity ratio of dexmedetomidine is 1620:1 compared to 220:1 for clonidine. Animal experiments have indicated that it has prominent anaesthetic effect. Studies in human volunteers have demonstrated clonidine like analgesic, sedative, sympatholytic and cardiovascular effects. In recent studies, dexmedetomidine has been shown to have clinically significant effects on anaesthetic requirements, haemodynamic responses induced by anaesthesia and surgery in patients. It has also been observed that an intraoperative infusion of dexmedetomidine combined with inhalation anaesthetics provided satisfactory intraoperative conditions without adverse haemodynamic effects and decreases emergence agitation in children.

The study was undertaken to assess the efficacy and safety of dexmedetomidine in attenuating sympathoadrenal response to tracheal intubation and to analyse reduction in intraoperative anaesthetic requirement.

MATERIAL AND METHOD: After local ethical committee approval and written informed consent, a total of sixty patients (n=60) of ASA grade I or II aged between 18-55 years of either sex scheduled for elective surgeries of around two to three hours under general anaesthesia were randomly assigned to one of the two groups, each containing 30 patients. Patients posted for emergency surgical procedures ,patients with cardiovascular or respiratory ,renal disorders ,diabetes, hypertension ,obesity, difficult airways, pregnant ,currently breast feeding women, history of sleep apnea, psychiatric disorder were excluded from the study.

On arrival in operating room the patients' base line heart rate, noninvasive blood pressure, oxygen saturation(SpO2), electrocard iography were recorded. An 18-gauge intravenous cannula was inserted and patients were pre-loaded with 5ml/kg of crystalloids. Both the group patients received premedication, intravenous dose of 0.004mg/kg Glyccopyrolate,0.15 mg/kg Ondansetron, 1µg/kg Fentanyl before induction of anaesthesia. Before induction of anaesthesia, the group-D patients were given Dexmedetomidine 1µg/kg loading dose over 10 minute while group-S, patients received same volume of normal saline over 10 minutes .Heart rate ,systolic blood pressure, diastolic blood pressure and oxygen saturation were recorded at the start of bolus drug injection ,at the end of bolus dose, and thereafter during intubation. Induction was achieved with 5mg/kg intravenous thiopentone sodium. Intubation was facilitated after giving 2mg/kg intravenous succinylcholine. Anesthesia was maintained with 3L/minute of fresh gas flow with 66% nitrous oxide with oxygen in closed circuit and muscle relaxation was maintained by0.8 mg/kg of vecuronium intermittent bolus. Isoflurane inhalation was started with 0.6% in both the groups. An increase in HR and/or MAP >20% from base line values was treated by increasing the Isoflurane concentration 0.2% increment as required .If there is no response within 5 minutes,1µg/kg Fentanyl was administered. Inj

Dexmedetomidine maintenance infusion of 0.6µg/kg/hr started in group-D and saline infusion in group-S in the same dose. Routine monitoring consisted of HR, NIBP, SpO2, ECG and ETISO, EtCO2 were recorded. The measurement were taken on the same arm throughout the study at the following times; base line ,after loading dose, after intubation, 5minutes,10minutes, 30minutes ,60min utes, 90minutes and 120 minutes, after infusion stopped, after reversal and extubation. Intra operative bradycardia (pulse rate<50/min) was treated with inj Atropine 0.6 mg intravenously. Intra operative hypotension was treated with intravenous crystalloids and by reducing the Isoflurane concentration and inj mephentermine. Isoflurane inhalation and inj Dexmedetomidine was stopped at the time of skin closure. At the end of surgery, the neuromuscular blockade was antagonised with inj neostigmine 0.05mg/kg and inj.glycopyrrolate 0.02 mg/kg. The extubation time was recorded together with the time to respond to simple verbal commands and the time for orientation. All the patients in both the groups were monitored for VAS and sedation for at least 4 hours after surgery. Post-operative pain intensity was assessed using a 0 to 11 point VAS score on which 0 indicated no pain and 10 indicated the worst pain. Post-operative sedation was assessed at regular intervals postoperatively using Ramsay Sedation Scale.

Statistical Analysis:

The sample size was determined by power analysis performed by pilot study. a sample size of 30 patients per group was required to detect a 20% change in heart rate, blood pressure with the power of 80%.Unpaired t- test was used to compare the study group and control group. Unpaired t-test was used to compare the variable before and after the intervention. The results were expressed as mean ±SD. P value<0.05 was considered as significant.

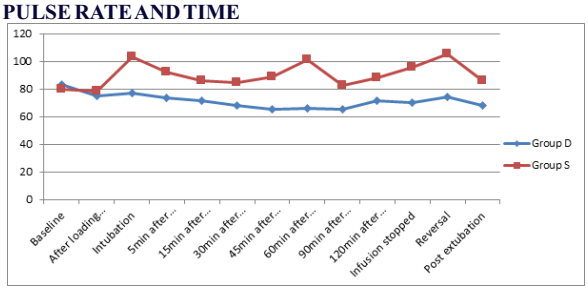
RESULTS:

Table 1: DEMOGRAPHIC DATA

Variables	Group D	Group S	P Value
Age			
Mean	40	40	Not Significant
Standard Deviation	5	4.9	
Gender Ratio			
M: F	9: 21	9:21	Not Significant
Weight			
Mean	53.43	57.93	Not Significant
Standard Deviation	8.42	9.92	
Duration Of Surgery			
Mean	99.23	99.97	Not Significant

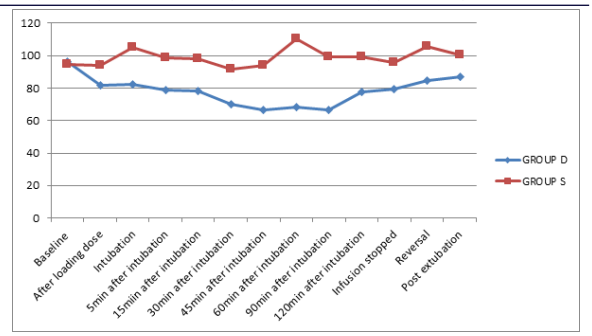
Table 1 shows the distribution of patients according to age, weight, and sex incidence in both groups with no significant difference.

Figure 1 GRAPH SHOWING REALTIONSHIP BETWEEN PULSE RATE AND TIME



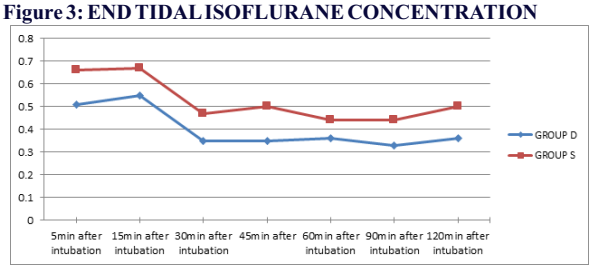
At intubation there was 1.77% rise in pulse from after loading dose in study group as compared to19.62 % in control group. At extubation there was 3.23% rise in pulse from base line in study group as compared to 9.53% in control group.Throughout intraoperative period Dexmedetomidine receiving patients have less heart rate in comparison to saline group

Figure 2: GRAPH SHOWING COMPARISON BETWEEN MEAN ARTERIAL BLOOD PRESSURE AND TIME.



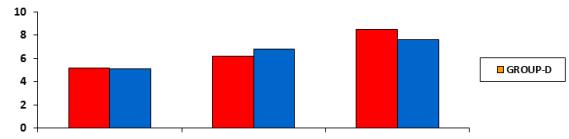
Throughout intraoperative period mean arterial blood pressure was significantly lower in group D as compared to Group S. From above observation it can be seen that after intubation and laryngoscopy there was an increase in pulse and blood pressure in both the group from baseline values. Maximum increase in pulse rate and blood pressure occur at intubation in both groups. But this increase statically significant in saline group patients. Post extubation at, a 3.97% rise in MBP was seen in the test group as compared to 9.35% in control group. There was increase in heart rate and blood pressure in response to extubation but in Group D patients this response in blunted by Dexmedetomidine.

Figure 3: END TIDAL ISOFLURANE CONCENTRATION



Mean Isoflurane concentration over intraoperative period is significantly less in group D as compared to group S.It can be seen that maximum difference in Isoflurane required is seen initially about 3 min – 10 min after intubation. Requirement in group D is 41.46% less in comparison to Group S.The overall mean end expiratory concentration of Isoflurane required during anesthesia maintained was 24.28% less in Group D in comparison to Group S.

FIGURE 4: RECOVERY PARAMETER:



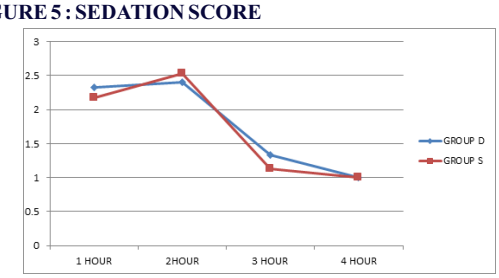
This time between stopping of anaesthesia , extubation time, response to verbal command and time for orientation were not significantly different in both groups.

TABLE-2: ANALGESIA REQUIREMENT

	GROUP-D	GROUP-S	P value
Total no of patient requiring inj Fentanyl	2/30	30/30	<0.05

The intraoperative requirement of Fentanyl was significantaly higher in control group.

FIGURE 5 : SEDATION SCORE



During postoperative period Ramsay sedation score is more in group D patients in comparison to saline group, but this difference is not statically significant.Two patients developed bradycardia and 3 Patients have hypotension in group D during the procedure. But these complications were treated with Atropine and fluid administration respectively.

DISCUSSION:

Laryngoscopy and tracheal intubation are considered as the most critical events during administration of general anaesthesia as it provoke transient but marked sympatho-adrenal response manifesting as hypertension and tachycardia.Hence a drug which can blunt both the heart rate and blood pressure response to laryngoscopy and intubation and intra operative surgical stress without having much adverse effect was required for this purpose. Dexmedetomidine is alpha-2 adrenoreceptor agonist which is pharmacologically active D-isomer of medetomidine .

The centrally acting alpha-2 adrenoreceptor agonist including Dexmedetonidine activate receptor in the medullary vasomotor center, reducing nor-epinephrine turn over and decrease central sympathetic out flow, resulting in alteration in sympathetic function. There by suppressing the haemodynamic response to intubation, extubation without any side effect. Additional effects results from the central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus cereleus in the brainstem. The activation of alpha-2 adrenergic receptor in the dorsal horn of the spinal cord inhibits the release of substance-P a nociceptive mediator instead of sub-p, anociceptive mediator, resulting in primary analgesic effect as well as potentiation of opoid induced analgesia.

In present study 60 patients of ASA physical status I or II, aged between 18 and 55 years, were randomly selected undergoing elective surgery and compared for haemodynamic stability, Isoflurane requirement and post-operative analgesia and recovery.

The patients in the two groups were comparable for age, sex, weight, ASA, duration of surgery and the difference between the two groups was not statistically significant($p>0.05$) as shown in table-1.In our study we found that bolus and intra-operative Dexmedetomidine infusion decreased haemodynamic response of various noxious stimuli and emergence from anaesthesia. Its haemodynamic effects are due to central sympatholytic action and cause a dose dependent reduction in a arterial BP and heart rate associated with decrease in serum nor epinephrine concentration.

- In our study At intubation there was 1.77% rise in pulse from the base line in study group as compared to 19.62% in control group as shown in figure-1.
- Intra-operatively, at 15 min post intubation pulse rate and mean blood pressure are significantly lower in Group D in comparison to Group S. The same trend was observed throughout intraoperative period as shown in figure 1&2.
- During extubation pulse rate value are increased by 3.23% in study group & 9.53% rise in control group as shown in figure-1 and mean BP rise 3.97% and 9.35% rise in respective group as shown in figure- 2.

Similarly, Bloor BC, Ward DS et al have observed a biphasic effect on hemodynamic after intravenous Dexmedetomidine in humans, an immediate increase in blood pressure(mediated by stimulation of peripheral stimulation of peripheral α-2 adrenoreceptors) followed by a longer lasting reduction in pressure caused by stimulation of α-2 adrenoceptors in central nervous system. Initial pressure effect is influenced by rate of intravenous infusion. They have observed this effect after giving 4μg/kg over 2 min period.

C.J. Lawrence et al did not observed such effect by infusing Dexmedetomidine over 5 min. similarly. In our study we have not observed this effect probably we have smaller dose (1μg/kg) given slowly over a period of 10 min M. Atm, Lehtinen et al 1991 where they found after administrating bolus dose of Dexmedetomidine there was decrease in heart rate after 10 min, post intubation increase blood pressure and heart rate was significantly less in Dexmedetomidine (0.6μg/kg/ hr) group than in the saline group. They found that, the post-intubation increase in heart rate was significantly less.

Jaakola et al showed that Dexmedetomidine attenuated the increase in HR and MAP during intubation.

Rao SH et al, 2012, observed that loading dose of Dexmedetomidine 1 μg/kg, followed by a continuous infusion of0.5μg/kg/hour provided a stable haemodynamic profile in the perioperative period and a blunted presser response to intubation and extubation. With its use, there was a minimal requirement for analgesics and inhalational agents. It had an acceptable recovery profile.

Varshali M Keniya, et al,2011, had observed Dexmedetomidine infusion in a dose of 1 μg/kg was given over 10 min before the induction of anaesthesia and was continued in a dose of 0.2-0.7 μg/kg/Hour until skin closure attenuated sympathoadrenal response to tracheal intubation and reduction in intraoperative anaesthetic requirement.

Yildiz, Munise et al, 2006 of Dexmedetomidine 1 μg/kg blunted the hemodynamic responses during laryngoscopy, and reduced Opioid and anaesthetic

The ability of α-2-adrenergic agonists to decrease anesthetic requirements has been previously described to their effect on central sympathetic transmission, since decrease in noradrenergic neurotransmission has been associated with a lowering of the MAC values. However some studies with Dexmedetomidine have suggested that other postsynaptic α-2 mechanism may also be involved. Sedation and analgesia probably account for the MAC- sparing effects of this class compound. Central α-2 adrenoceptors in the locus ceruleus and presumably by activating,nervous system and on to inhibition of release of receptors in the dorsal horn of' the spinal cord are likely involved in these effects. MAC reduction from Dexmedetomidine is much greater than with clonidine, presumably because of greater specificity of Dexmedetomedine for α2 adrenoceptors.

Lawrence CJ et al, 1997 found out that single pre-induction intravenous dose of Dexmedetomidine 2μg/kg reduces the intra-operative Isoflurane requirements.

Aanta, R Kanto et al. have documented decreased thiopental consumption'. was observed 47% Isoflurane MAC decrease after the association or intravenous Dexmedetomidine continuous infusion'. Khan found 35%-50% reduction in Isoflurane concentrations with either low or high doses of Dexmedetomidine

Aho et al ,reported that a continuous intraoperative Dexmedetomidine infusion can decrease the requirement of Isoflurane up to 90% in healthy patients.

Similarly the end–tidal Isoflurane concentration was significantly less in group-D as compared to group-s($p<0.05$) in our study. As shown in table no-5 The overall mean end expiratory concentration of Isoflurane required during anesthetic maintenance was 24.48% less in Group D as compared to Group S. Difference in Isoflurane requirement is maximum during first 10-15 min after intubation (41.50% less in Group D) This may be because attenuation of intubation response by Dexmedetomidine infusion so that less concentration of Isoflurane required to maintain the target haemodynamic level.

The pharmacodynamic effect of Dexmedetomidine may aid in reducing the concentration of anaesthetics used and preventing adverse effects such as hepatic and renal toxicity, severe myocardial depression, and the greenhouse effect.

Gurbetz A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of Dexmedetomdine reduces perioperative analgesic requirements. Can J Anaesth.

We found that Dexmedetomidine provide analgesia and reduce dose

requirement. The requirement of Fentanyl was reduced in the Dexmedetomidine group in our study.

Akshu et al suggest that Dexmedetomidine 0.5 µg/kg intravenously administered before extubation, was more effective in attenuating airway reflex responses to tracheal extubation and maintaining haemodynamic stability without prolonging recovery compared with Fentanyl 1µg/kg intravenously in these patients undergoing rhinoplasty. Turan et al found that Dexmedetomidine improved extubation conditions but did not prolong recovery in patients presenting for craniotomy.

In our study we observed comparable recovery parameter like extubation time, response to verbal command, and time for orientation in both groups. Time to eye opening on verbal commands was similar in both the groups.

After intravenously infusion, Dexmedetomidine has a rapid distribution phase, with a distribution half-life of approximately 120 minute which might be the explanation for early recovery.

POST OPERATIVE OBSERVATION:
SEDATION AND VAS SCORE

Study of D. P. Bhattacharjee, Sushil Nayek et al where they found that Dexmedetomidine caused sedation but did not cause any delay in recovery time. In another study of Judith E. Hall, tons Uhrich et all it was found that small dose Dexmedetomidine infusions caused sedation, impairment of memory and psychomotor per While they did find some amount of sedation by Dexmedetomidine in the course of our study, they did not find any memory loss or psychomotor impairment in any of their patients.

Dexmedetomidine provides sedation and analgesia with no accomp anying respiratory depression.

In our study, VAS for pain score was less in group D relative to group-S.

POST-OPERATIVE COMPLICATIONS:

C.J. Lawrence et al reported higher incidence of hypotension and bradycardia following intramuscular Dexmedetomidine. This may be because of higher intramuscular dose of Dexmedetomidine in their study.

Thus Dexmedetomidine infusion of 0.6µg/kg/min is not associated with significant complication and side effect in our study

No allergic phenomena were observed. During intraoperative period Atropine was required to treat bradycardia in 3 patients in Dexmedet omidine group and 2 patients develop hypotension in group S and corrected with intravenous fluid administration'

Limitations of study:

Because of lack of good clinical indices to determine the anaesthetic depth, haemodynamic end points were employed. It may be argued that these are not optimal for assessing depth, particularly when hemodynamic active drug is being studied and patients may actually have received unusually light anesthesia; however, this argument is not supported by the clinical observations in our study, since none of our patients complained of intraoperative awareness. Nevertheless, the possibility that the diminished Isoflurane requirements may have been partly the result of bradycardic effect of Dexmedetomidine cannot be totally excluded.

Another limitation in our study is that we have not measured plasma concentration of catecholamines as stress marker of sympathetic response to intubation and extubation.

CONCLUSION:

The loading dose of 1 µg/kg Dexmedetomidine, given over 10 min followed by continuous infusion of 0.6µg/kg/hr, as an adjuvant in general anaesthesia for elective surgeries provided a stable haemodynamic profile in perioperative period and effectively blunted pressor response to intubation and extubation, leading to minimal requirements for additional analgesics and potent inhalational agents. There was also an acceptable recovery profile.

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