Original Article

Effect of Dexmedetomidine Infusion in Analgesia and Intra-operative Hemodynamics in Major Surgeries under General Anesthesia : A Double Blinded Randomized Controlled Trial

Thingujam Sarjeet Singh[1], Ranjith Kumar Saravanan[2], Ettiyan Shanmugavalli[3]

Background : Events like laryngoscopy, tracheal intubation and extubation are critically involved in provoking transient, but significant sympathoadrenal response leading to hypertension and tachycardia. Any major surgeries would cause great tissue damage and have a high incidence of postoperative pain, complications and thus delay in recovery. There have been numerous ways to blunt the hemodynamic changes in response to these stressful conditions but not without unwanted side effects. Dexmedetomidine, a highly selective alpha-2 adrenergic agonist, is a sedative, analgesic and anxiolytic with unique sedation with no major respiratory depression. It provides conscious sedation and diminishes the intraoperative requirement of analgesics. It also provides a smooth transition from the time of reversal to the post-extubation period by suppressing the sympathetic activity of the central nervous system, leading to high-quality extubation with minimum hemodynamic changes. The aim of the study is to determine the effectiveness of dexmedetomidine on analgesia and maintaining a stable hemodynamic profile in the perioperative period.

Materials and Methods : Eighty patients of ASA I-III scheduled for elective surgeries lasting for 2-3 hours were randomly allotted into Group A to receive a bolus infusion of dexmedetomidine 1 mcg/kg/h, followed by infusion at the rate of 0.6 mcg/kg/hour intra-operatively and Group B to receive a normal saline infusion. Anesthesia was maintained with nitrous oxide in oxygen, atracurium and isoflurane. Hemodynamic parameters were recorded. Sedation was assessed by Ramsay Sedation Score immediately after extubation. Time of first rescue analgesia was recorded. Collected datas were analysed for statistical significance.

Results : The demographic variables, baseline mean Heart Rate (HR) & Mean Arterial Pressure (MAP) were statistically similar in both groups. Mean HR & mean BP were significantly lower in Group A than Group B throughout the procedure ($p<0.05$). Sedation was more in Group A in comparison to Group B in immediate post extubation ($p<0.05$). Group A has a longer duration till the first rescue analgesia of 64.88±7.72 min compared to Group B of 17.00±7.41min.

Conclusion : Dexmedetomidine is effective in maintaining hemodynamic stability and blunting the hemodynamic stress response induced by intubation and extubation. It can be administered as a loading dose of 1 mcg/kg prior to induction and as a maintenance infusion of 0.6 mcg/kg/hour throughout the procedure. Additionally, it extended the time frame for the first round of postoperative rescue analgesia. Therefore, dexmedetomidine can be used as a supplement to General Anesthesia in a variety of surgical procedures with minimal risk of adverse effects like Respiratory Depression.

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Key words : Dexmedetomidine, Hemodynamics, General Anesthesia, Postoperative Analgesia.

In 1940, Ried & Brace were the first to report the circulatory responses to laryngeal and tracheal stimulation in an anesthetized person[1]. Laryngoscopy and endotracheal intubation are usually necessary in individuals receiving General Anesthesia. These stimulate stimuli that cause sympathetic activation and catecholamine release, resulting in cardiovascular alterations, such as tachycardia, arterial hypertension, and arrhythmias[2,3]. These reflexes are mediated by the vagus and glossopharyngeal nerves, which convey afferent signals from the epiglottis and infraglotic areas and activate the vasomotor centre[4]. The stress responses induced by surgical injuries also cause hyper-stimulation of the sympathetic part of the Central Nervous System and an increase in anxiety hormones such as catecholamines and pro-inflammatory cytokines. Therefore, intra-operative management to modify the stress response is important for improving postoperative outcomes[5]. Although this reflex is transient, inconsistent and unpredictable, it can have negative effects, such as a hypertension crisis, myocardial ischemia, elevated Intracranial Pressure, and cerebrovascular accidents[6,7].

Editor's Comment :

- Dexmedetomidine infusion by decreasing Heart Rate produce stable intraoperative hemodynamics, smooth recovery during extubation and postoperative analgesia.

Department of Anesthesiology, Aarupadai Veedu Medical College & Hospital, Puducherry 607402
[1]MD, Postgraduate Trainee
[2]MD, Associate Professor and Corresponding Author
[3]MD, Associate Professor

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Dexmedetomidine is an imidazole derivative that binds highly selectively to alpha 2 receptors. They prevent the sympathetic terminal from releasing norepinephrine, which causes hypertension and bradycardia and promotes analgesia[8]. It has 7-8 times more affinity for alpha-2 receptor than clonidine. It has a unique property as a sedative as it has limited respiratory depression[9]. In the recent few years, IV Dexmedetomidine has been extensively reckoned for its efficiency in enhancing hemodynamic composure before, during and after surgical procedures and postoperative pain relief in patients undergoing surgical procedures under general anesthesia[10].

Dexmedetomidine when given as pre-anesthetic medication prior to induction and infusion during surgery, helps in attenuation of pressure response to diverse noxious stimuli and maintains hemodynamic composure. But its tranquilizing property delays recovery after surgery[11]. Frequently mentioned dose in the literature is a bolus of 1 mcg/kg/hour over 10 min, come next by an infusion of 0.2 to 0.7 mcg/kg/hour[12]. Apart from using as an adjunct, intra-operative dexmedetomidine lowers the Minimum Alveolar Concentration (MAC) of inhaled anesthetics leading to no overt evidence of intra-operative awareness[13]. This randomized controlled trial was devised to determine the clinical potency of Dexmedetomidine in maintaining stable hemodynamics when used in conjunction with general anesthesia during major elective surgery.

Material and Methods

After getting the Institutional Ethical Committee approval, with IEC No. AV/IEC/2020/125, CTRI registration was done under registration no. CTRI/2021/01/030676. Informed written consent was acquired. The study was executed on randomly selected 80 adults who fall under the American Society of Anesthesiologists (ASA) physical status I – III and planned for major surgeries lasting for 2-3 hours like modified radical mastectomy, radical neck dissection, resection anastomosis, staging laparotomy, etc under General Anesthesia except for laparoscopic surgeries. Utilizing a computer-generated arbitrary number procedure, the patients were split up into two groups, A and B. Intravenous solutions containing either Dexmedetomidine or 0.9% saline were concocted by an Anesthesiologist (not a part of the researcher's team). Dexmedetomidine, 2 ml ampoules containing 100 mcg/ml, was mixed with 48 ml of normal saline to get a concentration of 4 mcg/ml. A 50 ml amount of 0.9% saline solution was prepared for each subject in control group. As a part of the standard ASA monitoring, Non-invasive Blood Pressure, Electrocardiography, peripheral oxygen saturation and end-tidal carbon dioxide were all attached to the patient. Patients in Group A were infused a loading dose of Dexmedetomidine (1 mcg/kg) within 10 min before the induction of anesthesia, whereas patients in Group B were administered the similar volume of 0.9% saline at the similar infusion rate in the same duration.

Following the loading dose, all of the patients in both groups were premedicated according to the institutional protocol with IV Ondansetron 0.08 mg/kg, IV Midazolam 0.02 mg/kg and IV Glycopyrrolate (0.004 mg/kg). In 2mcg/kg of IV fentanyl was administered as a preoperative analgesic. Induced with propofol at doses of 2-3 mg/kg. In 2 mg/kg of intravenous succinylcholine was used to aid intubation. Adequate muscle relaxation was maintained with repeated dosage of atracurium (0.5 mg/kg) by using capnograph. The patients were placed on mechanical ventilation with a tidal volume of 6-8 ml/kg, at the rate of 14 breaths/min and fresh gas flow of 3 L/min that contained 70% N_2O in O_2. Isoflurane was initiated at a rate of 0.6% in both groups. In 0.6 mcg/kg/hr injection Dexmedetomidine maintenance infusion was started in Group A while Group B was given Injection saline infusion at the same dose as Dexmedetomidine infusion. The following timelines were used to assess Heart Rate (HR) and Mean Arterial Pressure (MAP): baseline, after the loading dosage, immediately after intubation, every 10 min for the first hour, during the second and fourth postoperative hours, and immediately after extubation.

To alleviate intraoperative hypotensive episodes, crystalloids were administered intravenously and the concentration of isoflurane was decreased. Dexmedetomidine infusion was terminated along with the conclusion of skin closure and volatile agent was halted ten minutes before the termination of the procedure. Reversal achieved with 0.05 mg/kg of neostigmine and glycopyrrolate (0.01 mg/kg). All patients were extubated, transferred to the recovery area and kept under observation for up to 4 hours following surgery, while their hemodynamic parameters, postoperative analgesia, drowsiness, and time of first rescue analgesia were documented. Immediately after extubation, the Ramsay Sedation Scale (RSS)[14] was used to assess the level of sedation. RSS score >3 was termed Excess sedation.

A 10-point Visual Analog Scale (VAS), with 0 representing no pain and 10 representing the most agonizing pain imaginable, was used to measure the degree of postoperative pain. If the VAS score >3, tramadol (100 mg) was administered intravenously.

Emesis was treated with IV ondansetron (4 mg).

Statistical Analysis :

Categorical variables were expressed as frequency and percentages. Continuous variables were synopsized as mean ± Standard Deviation. Normality of the data were assessed using Kolmogorov Smirnov's test. Independent 't' test was used to compare the continuous variables such as HR, MAP between the comparing groups. The p value less than 0.05 was considered as statistically significant. SPSS software version 28 was used for data analysis.

Results

In this double-blinded, randomized study, 80 adults in total were allowed into two groups. Group A: IV bolus of Injection Dexmedetomidine (1 mcg/kg), following with infusion of 0.6 mcg/kg/hour as a maintenance dose. Group B: IV bolus dose of 0.9% saline with a maintenance infusion later.

The trial was conducted on adults posted for conventional major surgeries done under General Anesthesia. The comparison was done using the bolus dose followed by an infusion of Dexmedetomidine (Group A) or 0.9% saline (Group B) for their efficacies in attenuating stress response to endotracheal intubation. The following were also evaluated: intra-operative hemodynamic stability, obtunding the stress response of extubation, post-operative recovery characteristics, and postoperative analgesia. Table 1 demonstrates zero significant discrepancies in either group's age, sex, BMI, ASA grade or surgical time ($p>0.05$). Surgery took an average of 145.75 ± 24.19 min in Group A and 144.50 ± 22.38 min in Group B.

The baseline MAP in Group A was 96.40 ± 6.74 while in Group B, it was 94.25 ± 6.66. The baseline mean HR in group A was 84 ± 10.09 in Group A and 81.78 ± 10.16 in Group B (Table 2). So there was no significant difference between the Groups.

In comparison to Group B, a substantial decrease in HR was observed in Group A ($p<0.05$) following the loading dosage, after intubation, right after extubation, 2nd hour in the PACU and 4th hour in the PACU, as shown in Table 2. The MAP greatly lessened in group A compared to Group B after the loading dosage, during intubation, immediately following extubation, and during the second and fourth hours in the PACU. The first rescue analgesia was administered at 64.88 ± 7.72 min in Group A and 17.00 ± 7.41 min in Group B, which is statistically relevant ($p<0.05$). In Group A, 12 patients had sedation scores that were on greater side, but none of them had excessive sedation. Therefore, the values had no significance level.

Table 1 — *Comparison of Demographic Variables*

Demographic variables	Group A	Group B	P values
Age	43.00±12.19	44.08±12.30	0.348
BMI	21.97±2.9	21.69±3.25	0.345
Duration of Surgery(min)	145.75±24.19	144.50±22.38	0.406
Sex (Male/Female)	14/26	12/28	0.633
ASA (I / II / III)	11/14/15	11/11/18	0.729
RSS after extubation (1/2/3)	10/19/12	17/17/5	0.902

BMI = Body Mass Index, SD = Standard Deviation,
ASA = American Society of Anesthesiologists,
RSS = Ramsay Sedation Scale

Discussion

The present study showed that pre-operative bolus and intra-operative infusion of Dexmedetomidine are beneficial in lowering stress reactions to diverse unpleasant stimuli in patients undergoing major procedures conducted under general anesthesia. Since a substantial reduction in mean HR and MAP in comparison with placebo was observed throughout the procedure, Dexmedetomidine (0.6 mcg/kg/hour) infusion was beneficial in decreasing HR and BP brought on by the stressful events. ($p<0.05$). Its hemodynamic effects occur through peripheral vasoconstriction and central sympatholysis.[15] It decreases arterial pressure and Heart Rate and reduces serum norepinephrine concentrations in a dose-dependent manner. Without any negative effects, it alters sympathetic activity. It also reduces physiological responses to endotracheal intubation and extubation. It accomplishes this by increasing norepinephrine metabolism, stimulating vasomotor centre receptors, and inhibiting sympathetic outflow. Additional effects are produced by centrally stimulating parasympathetic discharge and suppressing sympathetic discharge from the locus coeruleus. Numerous studies have shown that dexmedetomidine reduces the hemodynamic reactions to endotracheal intubation during general anesthesia[16]. The alteration in metabolic and immune system functions brought by surgical trauma include Sympathetic Nervous System activation, increased pituitary hormone production, insulin resistance and the release of inflammatory cytokines[17]. An inimical postoperative outcome, such as postoperative hypertension, vascular graft blockage and the emergence of morbid cardiac events, were all

Table 2 — *Duration of First Rescue Analgesia and Sedation status*

Variables	Mean ± SD		P Values
	Group A	Group B	
Duration of first rescue analgesia	64.88±7.72	17.00±7.41	<0.001*
Ramsay sedation at the time of extubation	1.88±0.72	1.88±0.76	0.5

*P < 0.05 : Statistically Significant

associated with intra-operative catecholamine concentrations[18]. Surgical results were enhanced by improved organ function caused by a reduction in the sympathetic hormonal response to acute unpleasant stimuli. Owing to the possible positive impacts on postoperative prognosis, there has been a great deal of interest in altering the intraoperative stress response[19]. Patients who were administered dexmedetomidine had lower levels of epinephrine and norepinephrine during and after surgery, maintained their blood pressure levels, and experienced less pain in the primary postoperative phase.

Dexmedetomidine, a extremely selective alpha-2 adrenergic receptor agonist, has negligible effects on breathing and has sedative, analgesic and opioid-sparing effects. It activates presynaptic 2 receptors, which prevent sympathetic synaptic locations from releasing epinephrine and norepinephrine[20]. In patients undergoing surgery, Dexmedetomidine enhanced hemodynamic stability and decreased the amount of circulating plasma catecholamines in a dose-dependent manner. Dexmedetomidine has also been shown to reduce systemic inflammatory reactions in several circumstances, including cardiac bypass, severe sepsis and surgery[21].

According to Basantwani, *et al*[22] intra-operative HR and MAP in the Group receiving a 0.5 mcg/kg/hour Dexmedetomidine infusion were found to be lesser than baseline values and corresponding values compared to those in the group receiving normal saline. A higher percentage of patients in the group receiving 0.9% saline infusion had got to receive rescue propofol and fentanyl (36.6% and 30% *versus* 6.6% and 3.3%, respectively). The recovery profile was better in the Dexmedetomidine-infused category.

The observations of the current trial are again supported by the findings of the trial conducted by Bala, *et al*[23]. The intervention group was administered a bolus dose of Dexmedetomidine(1mcg/kg) over 10 min, followed by 0.5 mcg/kg/hour infusion. Normal saline was administered to the control group in a similar fashion. They observed an increase in HR and BP following direct laryngoscopy, endotracheal intubation, insertion of a nasal speculum and extubation in both groups, but it was more profound in the control group. The need for analgesics, muscle relaxants and volatile agents during the intra-operative period was much less in the intervention group. The time of emergence from anesthesia and VAS score at the time of emergence were also negligible in the Dexmedetomidine group.

Dexmedetomidine and remifentanil's effects on hemodynamic stability, sedation, and postoperative pain management were investigated by Jung, *et al*[24] in 50 patients scheduled for total laparoscopic hysterectomy who were randomly assigned to receive either remifentanil (0.8 to 1.2 mg/kg) over 1 min followed by 0.05 to 0.1 mg/kg/min or Dexmedetomidine (1 mg/kg) over ten minutes followed by 0.2 to 0.7 mg/kg/hr infusion. In the postoperative room, the BP and HR were considerably curtailed in the Group receiving Dexmedetomidine compared to the Group receiving remifentanil. When comparing the postoperative hemodynamic stability between Dexmedetomidine and remifentanil, the doses utilized in this study showed a clear advantage for Dexmedetomidine.

The findings of this study are further supported by Panchgar, *et al*[25] who investigated the efficiency of Dexmedetomidine in preserving hemodynamic stability throughout the peri-operative phase in randomized patients undergoing Laparoscopic Surgery. They came to the conclusion that the Dexmedetomidine group successfully obtunded the hemodynamic reactions to the stressful situations. The demand for postoperative analgesics was incredibly less in the intervention group. No adverse effects reported outside the two instances of bradycardia in this category.

There have been few limitations in our study. First, we conducted this study on different types of surgeries ranging from modified radical mastectomy to staging

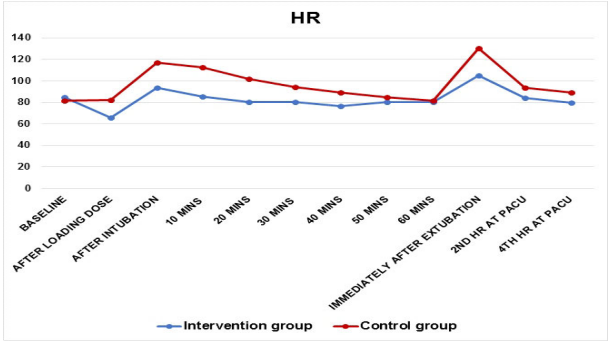

Fig 1 — Graphical representation of the Heart Rates in both groups

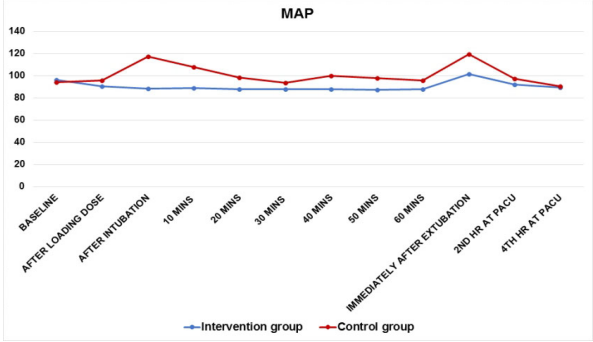

Fig 2 — Showing comparison of Mean Arterial Pressure in both groups

laparotomy. So, it could have been done in more standardized manner. Second, we excluded patients with Cardiovascular diseases. So it's not appropriate to comment on the effects of Dexmedetomidine on these types of patients. Third, the comparison was done between Dexmedetomidine and a placebo which resulted in the obvious outcome. As a result, we can contrast the potency of Dexmedetomidine with that of other medications in a future part of this study.

Conclusion

It is concluded that Dexmedetomidine is effective in maintaining hemodynamic stability and blunting the hemodynamic stress response induced by intubation and extubation. It can be administered as a loading dose of 1 mcg/kg prior to induction and as a maintenance infusion of 0.6 mcg/kg/hour throughout the procedure. Additionally, it extended the time frame for the first round of postoperative rescue analgesia. Therefore, Dexmedetomidine can be used as a supplement to General Anesthesia in a variety of surgical procedures with minimal risk of adverse effects like Respiratory Depression.

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