

## Effect of dexmedetomidine infusion on stress induced blood glucose levels and intraoperative sevoflurane requirement

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### Abstract

**Introduction:** Dexmedetomidine has been shown to blunt the stress response to surgery and reduce the consumption of inhalational anaesthetic agents. Hence, we designed this study to observe the effects of IV Dexmedetomidine infusion on stress-induced blood glucose levels and intra operative Sevoflurane requirement during laparoscopic surgery.

**Materials and Methods:** Sixty patients between the ages of 18-60 years, of either gender, ASA Grade I & II, posted for elective laparoscopic surgical procedures under general anaesthesia were divided into two groups of 30 each. Group D received loading dose of Inj. Dexmedetomidine at 1µg/kg diluted to 50 ml and given over 10 minutes; followed by maintenance with 0.5µg/kg/hour, till the end of surgery. Group P received similar volume of normal saline. Anaesthesia was maintained with Nitrous oxide in oxygen (50:50) and Sevoflurane keeping BIS 40 - 60. Serial blood glucose levels, sevoflurane requirement by Dion's method, extubation time, sedation score and adverse effects were observed. The data was analyzed using student t test.

**Results:** Blood glucose levels at first hour post operatively in group P and in group D, were 136.7±6.30 mg/dl and 103.8±8.28 mg/dl respectively (P<0.0001). There was 27.07% rise in group P and 2.89% fall in group D from baseline value. Mean first hourly Sevoflurane consumption in group P and in group D were 11.22±1.14 ml and 8.34±0.88 ml respectively (p<0.0001) (25.61% reduction in group D).

**Conclusion:** IV Dexmedetomidine infusion was effective in attenuating stress induced blood glucose levels and it also reduced Sevoflurane requirement without affecting the time for extubation.

**Keywords:** Dexmedetomidine, Stress induced blood glucose levels, Dion's method, Sevoflurane consumption.

### Introduction

Alpha ( $\alpha$ )-2 adrenergic receptor (AR) agonists are the centre of interest in Anaesthesiology since last two decades for their sedative, anxiolytic, analgesic and sympatholytic properties.<sup>1,2</sup> The first member of this group; Clonidine; which was introduced in 1960 as nasal decongestant, was later used as an adjuvant for general as well as regional anaesthesia.<sup>1,2</sup> After the discovery of Clonidine, a more potent Alpha( $\alpha$ ) -2 agonist Medetomidine,<sup>3</sup> and its stereoisomer Dexmedetomidine were discovered.

Dexmedetomidine has been described as a 'Wonder Drug'<sup>4</sup> due to its multiple roles in anaesthesia practise.

Stress response to surgery and anaesthesia is not only manifested as changes in pulse rate and blood pressure but also by metabolic, neurohormonal and immunological changes.<sup>5,6</sup> Therefore, various indicators like blood glucose, serum cortisol, Interleukin-6, plasma nor-epinephrine levels have been used to quantify the stress response and their attenuation by dexmedetomidine has been demonstrated.<sup>7,8</sup>

In addition to its analgesia sparing property,<sup>9,10</sup> intravenous administration of Dexmedetomidine during general anaesthesia is reported to decrease the minimum alveolar concentration (MAC) and intraoperative requirement of volatile anaesthetic agents.<sup>11</sup>

This clinical study; therefore, aims to demonstrate the effect of intravenous Dexmedetomidine administration on stress induced blood glucose levels and intra operative Sevoflurane requirement. It also includes assessment of perioperative hemodynamic stability, time for tracheal extubation and post operative sedation levels.

### Materials and Methods

After obtaining institutional ethical and scientific research committee approval; this prospective, randomised, single blind, placebo-controlled clinical trial was conducted in department of Anaesthesiology, Government Medical College and SSG Hospital Vadodara during November 2014 to November 2015. 60 patients of age group 18 to 60 years, of either gender, American Society of Anaesthesiologists (ASA) grade I and II, posted for laparoscopic intra-peritoneal surgeries of 1-2 hours duration with minimal expected blood loss were enrolled. Patients on  $\alpha$ -2 agonists or antagonists,  $\beta$  blockers, calcium channel blockers, digoxin or any other anti hypertensive agent, psycho active medications, pregnant and breast feeding mothers, ASA grade III or IV patients and those unwilling to participate in the study were excluded. After thorough pre anaesthetic check up and routine investigations, selected patients were informed about the motto of our study in local language and a written

informed consent was taken after ensuring their willingness to participate in the study.

After ensuring adequate fasting, patient was shifted to operation theatre, multipara monitor was attached to note the baseline pulse rate, blood pressure, spo<sub>2</sub>; and BIS, attached to note baseline consciousness. 18G IV cannula was secured and Ringer Lactate at 5ml/kg/hour was started. All patients received premedication Inj. Glycopyrrolate 0.2 mg/i.m 45 minutes before surgery; and before induction, Inj. Ondansetron 4mg/i.v, Inj.

Ranitidine 50mg/ i.v, Inj. Fentanyl 2mcg/kg/i.v were given. Patients were randomly divided (Randomisation by computer method using www.randomiser.org) into 2 groups: Group (D) patients received loading dose of Inj. Dexmedetomidine 1µg/kg/10min diluted to 50ml with Normal Saline, given before induction, followed by maintenance dose 0.5µg/kg/hour till the end of surgery; and Group (P) patients received Normal Saline in a similar manner.

**Table 1: Dexmedetomidine loading dose and maintenance dose calculation**

Actual weight(kg)	Taken weight as(kg)	Loading Dose (Given over 10 minutes)		Maintenance Dose	
		Dose of Dex(µg)	Infusion volume(ml)	Dose of Dex(µg)	Infusion rate (ml/hr)
41-45	40	40	10	20	5
46-50	50	50	12.5	25	6.25
51-55	50	50	12.5	25	6.25
56-60	60	60	15	30	7.5
61-65	60	60	15	30	7.5
66-70	70	70	17.5	35	8.75

#### Syringe infusion pump



Patients were pre oxygenated for 3 minutes with 100% oxygen, Inj. Propofol 1.5mg/kg given as boluses of 20-30mg till loss of eyelash reflex response and BIS dropped to 50. Inj. Succinyl choline 1.5 mg/kg/i.v given and ventilation continued. Once fasciculation disappeared from toes, patients were intubated with appropriate size cuffed portex endotracheal tube. Tube connected to Bain's circuit, bilateral equal air entry confirmed and tube was fixed adequately. Anaesthesia was maintained with nitrous oxide in oxygen (50:50), at 3Litres/minute, with Inj. Vecuronium bromide 0.1mg/kg as loading dose and 0.025mg/kg as top-up when required (last dose 25minutes before expected completion of surgery) and Sevoflurane titrated to maintain BIS 40-60. Anaesthesia machine Drager Fabius was used. End tidal carbon dioxide (EtCO<sub>2</sub>) and intra abdominal pressure were maintained between 35-45mm of Hg and 12-14 mm of Hg respectively. At the end of surgery nitrous oxide, Sevoflurane, Inj. Dexmedetomidine infusion was stopped. Patient was ventilated with 100% oxygen till onset of respiratory efforts, after which reversal of residual neuro muscular

blockade was done with Inj. Neostigmine 50mcg/kg i.v and Inj. Glycopyrrolate 10mcg/kg i.v. Extubation was done after ensuring adequate response to verbal commands, breathing effort and muscle tone. Patient was then shifted to recovery room (PACU).

Blood glucose levels were measured from patient's fresh capillary whole blood using glucose strip test<sup>8</sup> at following intervals: Baseline (before Dexmedetomidine bolus), 30 minutes after intubation, 1<sup>st</sup> and 2<sup>nd</sup> hour post operatively. Hourly Sevoflurane requirement was calculated by Dion's method as follows: Usage of volatile anaesthetic agent (ml) = Dialed concentration (%) x duration at set concentration (min) x Total fresh gas flow (litre/min) x Molecular mass (mg) / 2412 x Density (g/ml).<sup>12</sup> The fixed values in this formula include- Total FGF (3 ltr /min), Molecular mass of Sevoflurane (200.055 mg) and Density of Sevoflurane at 21°C (1.52 g/ml). The changing values were Dialed concentration and Duration at set concentration. Substituting the fixed values, this equation can be rewritten as: Amount of liquid Sevoflurane used (ml) = 0.00273PT, (P = Dialed concentration, T = Time in seconds).<sup>13</sup> Patient's pulse rate (bpm), oxygen saturation (%), systolic and diastolic blood pressure (mm of Hg) were noted at following intervals: Baseline (before bolus), 10 minutes after bolus, 1 minute after induction, after laryngoscopy and intubation, post pneumoperitoneum (PP) at 0, 15, 30, 45, 60, 75, 90, 105, 120 minutes and post extubation (PE) at 0, 15, 30, 60 and 120 minutes respectively.

The time for tracheal extubation was taken from stoppage of anaesthetic agents and Dexmedetomidine to the time when patient was extubated. Ramsay sedation score (table 2) at 0 and 60<sup>th</sup> minute post extubation was

noted. Duration of surgery and anaesthesia were recorded.

**Table 2: Ramsay sedation score**

Score	Response
1	Anxious or restless or both
2	Co operative, oriented and tranquil
3	Responding to commands only
4	Brisk response to light glabellar tap or loud auditory stimulus
5	Sluggish response to light glabellar tap or loud auditory stimulus.
6	Patient exhibits no response.

Adverse effects were noted and adequately treated as shown in table 3.

**Table 3: Definition of Adverse effects and their management**

Adverse effects	Treatment
Bradycardia (PR<50bpm or Fall in PR> 20% from baseline value)	Inj. Atropine 0.6mg IV
Tachycardia (PR>120bpm or Increase in PR> 20% from baseline value)	Increase in Sevoflurane concentration. → Inj. Metoprolol 5 mg IV
Hypotension (SBP < 80 mm of Hg /Fall in SBP > 20% from baseline value)	Reduce inspired Sevoflurane conc. → 200ml fluid bolus → Inj. Ephedrine 5-10 mg bolus.
Hypertension (SBP > 140 mm of Hg or rise in SBP > 20% from baseline value)	Increase inspired Sevoflurane conc. → Inj. Nitroglycerine IV infusion
Nausea / vomiting	Inj. Metochlopramide 10 mg IV
Heavy Sedation (RSS 4 or more)	Oxygenation
Dryness of mouth	Wetting of lips

### Statistics

Sample size was calculated using 'blood glucose levels' as primary criteria,<sup>14</sup> (In our reference paper, significant difference in mean blood glucose levels was observed during 1<sup>st</sup> hour post-operatively) with confidence interval 95% ( $\alpha$  error 0.05), power 90% ( $\beta$  error 0.1) was 20 in each group. For better sensitivity we included a total of 60 patients with 30 in each group. Statistical-analysis was done using Medcalc software 12.5.0.0 version, with T-test and Chi-square test used for parametric and non-parametric data respectively and

results expressed as mean±SD. *P* value less than 0.05 was considered as statistically significant(\*), less than 0.01 was highly significant (\*\*) and values <0.001 was very highly significant (\*\*\*)

### Results

Both the groups were comparable with respect to demographic data like age, gender, body weight, ASA grade, duration of surgery and anaesthesia.

**Table 4: Demographic data**

Parameters	Group P	Group D	P value
Age (yr) (mean ±SD & range)	38.77±10.15 (21-56)	35.73±11.18 (19-60)	>0.05
Gender: Male Female No. Of patients (%)	18(60%) 12(40%)	15(50%) 15(50%)	>0.05
Weight (kg) (mean±SD & range)	60.1±5.50 (50-73)	58.37±6.25 (40-68)	>0.05
ASA: 1 2 No. Of patients (%)	21(70%) 9(30%)	23(76.6%) 7(23.3%)	>0.05
Duration of surgery (min) (mean±SD)	97.33±6.21	97.93±5.03	>0.05
Duration of anaesthesia (min) (mean±SD)	110.76±5.06	109.06±4.01	>0.05

The blood glucose level was very highly significantly ( $p < 0.0001$ ) lower in Group D as compared to Group P at all intervals except baseline. Laryngoscopy and intubation caused a rise in blood glucose levels by 45.2% in group P, while the rise was 9.69% in group D. 1<sup>st</sup> hour post operatively, the blood

glucose level was 27.07% higher than the baseline in group P, but group D showed 2.89% fall from the baseline value. 2<sup>nd</sup> hour post operatively, the blood glucose level remained 11.05% higher than the baseline value in group P, but group D showed a reduction by 0.25% (Fig. 1)

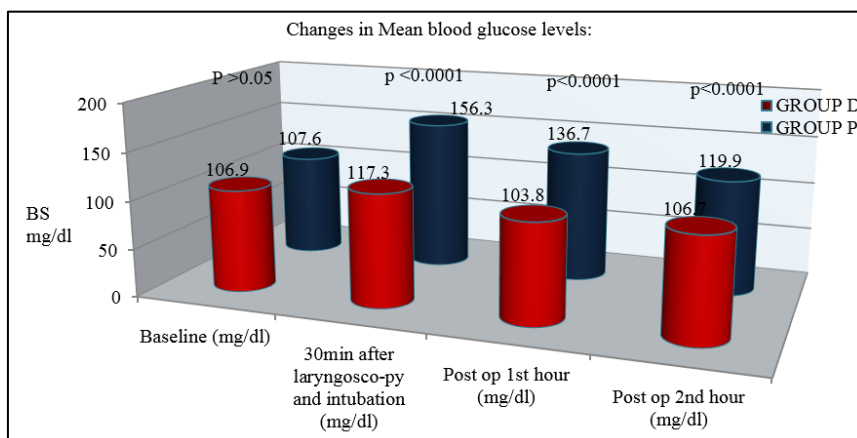


Fig. 1: Changes in mean blood glucose levels

Compared to Group P, Group D patients showed statistically significant reduction in hourly Sevoflurane requirement, as calculated by Dion’s formula

( $p < 0.0001$ ). There was 25.61% and 21.47% reduction in Sevoflurane requirement during 1<sup>st</sup> and 2<sup>nd</sup> hour in Group D as compared to Group P. (Fig. 2)

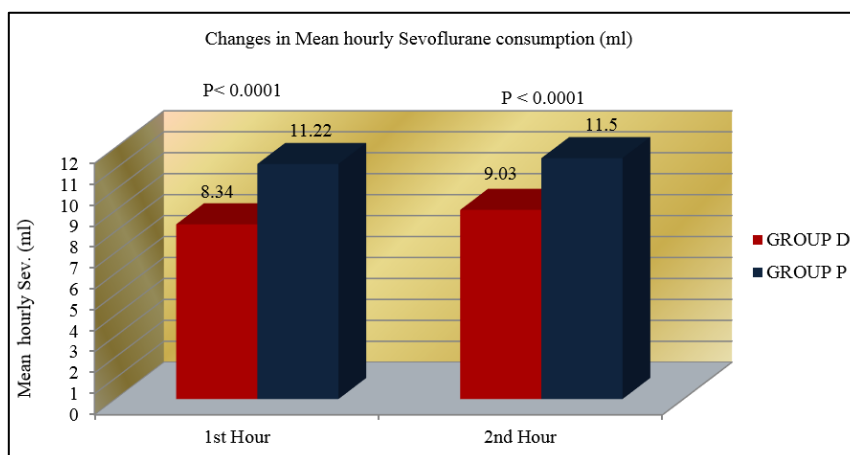


Fig. 2: Changes in mean hourly sevoflurane consumption (ml)

Mean pulse rate was very highly significantly lower in group D from 10 minutes after bolus to 75<sup>th</sup> minute post pneumoperitoneum ( $p < 0.0001$ ), thereafter till 30<sup>th</sup> minute post extubation it remained significantly lower in Group D ( $p < 0.05$ ). Critical events like laryngoscopy, intubation and pneumoperitoneum

caused some rise in pulse rate compared to post induction values in Group D, but the values were still highly significantly lower than Group P ( $p < 0.01$ ). (Fig. 3)

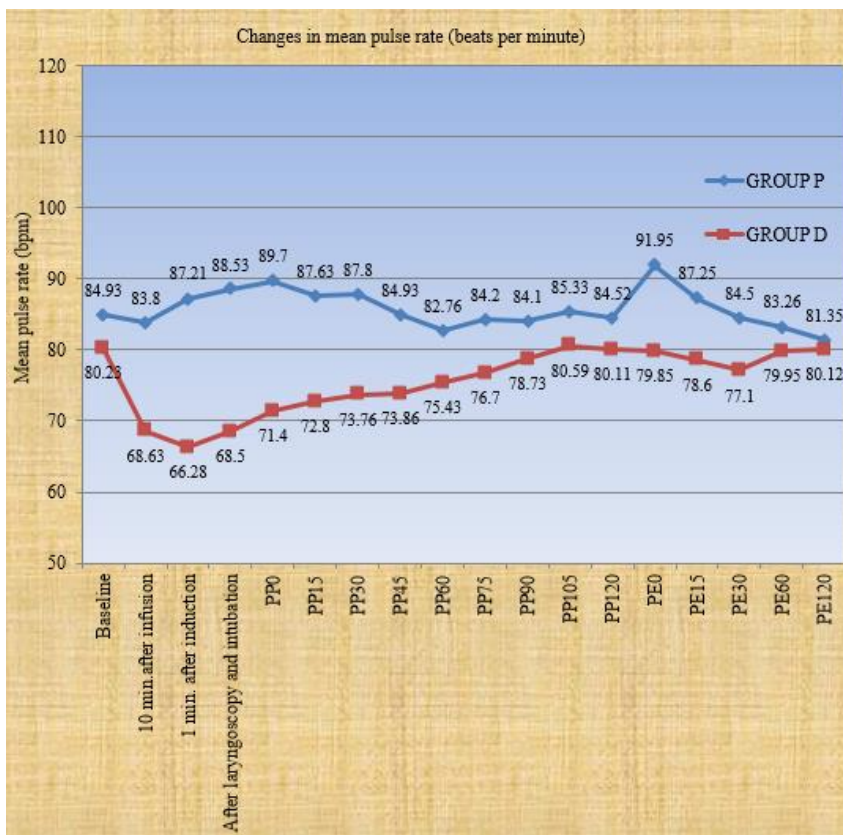


Fig. 3: Changes in mean pulse rate (bpm)

Tracheal extubation time and mean Ramsay Sedation scores were comparable in both the groups (p>0.05)

Table 5: Extubation time and Post –operative mean Ramsay sedation scores (mean±SD)

Parameter	Group P	Group D	P value
Extubation time (min)	5.36±1.17	5.83±1.09	>0.05
Mean Ramsay sedation score Post operative			
0 minute	3.52±0.53	3.11±0.40	>0.05
60 minutes	3.83±0.21	3.54±0.52	>0.05

The incidence of various adverse effects was comparable in both the groups. (Fig. 4)

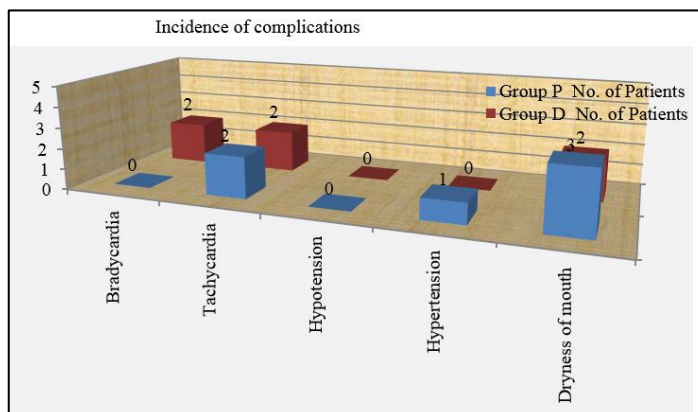


Fig. 4: Incidence of complications

Bradycardia was observed in two patients in group D, which was relieved by Inj. Atropine 0.6mg i.v, while Hypertension was observed in one patient of group P; though, not persistent.

### Discussion

Laparoscopic surgeries are preferred now-a-days due to its various advantages like less trauma, less pain, quicker recovery and shorter hospital stay; hence we selected this surgery for the study. Anaesthesia and surgical procedures like laryngoscopy, intubation, extubation, reverse Trendelenburg patient positioning, pneumo peritoneum, carbon di oxide insufflation are associated with stress response (Dr. Manorama Singh 2003).<sup>5</sup> This causes neuroendocrine, cytokine release which increases catecholamine and steroid levels, with predictable metabolic consequences (O'Riain SC et al 2005).<sup>15</sup>

Stimulation of hypothalamus, during stress, responds by causing ACTH release, resulting in sudden increase in cortisol.<sup>6</sup> This rapidly mobilises the amino acids, fat; to form glucose, causes insulin resistance; thereby increasing blood glucose upto 50% above normal,<sup>5</sup> making glucose available for energy and synthesis of other compounds needed by different tissues.<sup>16</sup> Hence, estimation of blood glucose serves to be a reliable indicator for indirect assessment of stress response and its modulation by pharmacological agents like alpha-2 agonists.<sup>8</sup>

Though such stress response is considered as homeostatic defence mechanism for adaptation and developing resistance to noxious stimuli, the continuous hyper metabolic state may result in exhaustion of essential components of the body causing fatigue, decreased resistance, delayed ambulation and increased morbidity and mortality.<sup>5,6</sup> It could also be life threatening to patients with co morbidities like obesity, hypertension, diabetes mellitus, renal insufficiency, liver disease, geriatric age group.

Alpha-2 receptor agonists including Clonidine and Dexmedetomidine have been extensively used in clinical practice. Dexmedetomidine differs from

Clonidine in two aspects - one, it is more potent and receptor specific and secondly it is easy to titrate.<sup>17</sup>

Higher doses of Dexmedetomidine have been found to produce adverse biphasic cardiac response i.e. hypertension followed by hypotension,<sup>18</sup> while very low doses fail to attenuate stress response to critical events.<sup>19</sup> Dexmedetomidine has been used as single bolus dose as well as bolus followed by infusion.<sup>20,21</sup> Keniya VM et al 2011<sup>22</sup> found that Dexmedetomidine infusion in a dose of 1mcg/kg over 10 minutes followed by infusion of 0.2-0.7 mcg/kg/hr can attenuate sympatho-adrenal response to tracheal intubation. Gupta K et al 2013<sup>8</sup> used a single bolus dose of IV dexmedetomidine given in 10 minutes before induction while Harsoor SS et al 2014<sup>14</sup> and Yacout AG et al 2012<sup>7</sup> used Dexmedetomidine in a loading dose of 1mcg/kg over 10 minutes before induction followed by 0.5 mcg/kg/hr till end of surgery. Since the distribution half life of Dexmedetomidine is about 9 minutes and the drug should be infused slowly to avoid the biphasic response, we also used similar dose schedule as used by Harsoor S S et al 2014 and Yacout A G et al 2012.<sup>7,14</sup>

Our study shows that in Group P, the changes in mean blood glucose levels (45.20% rise from baseline 30 minutes after intubation, 27.07% rise during 1<sup>st</sup> hour post operatively and 11.05% rise during 2<sup>nd</sup> hour post-operatively) co relates with studies by Yacout AG et al 2012, Gupta K et al 2013<sup>7,8</sup>. In Dexmedetomidine group, though there was a significant rise ( $p < 0.05$ ) in blood glucose at 30 minutes post laryngoscopy and intubation, but it was much less than group P (9.69% versus 45.2%; inter group  $p < 0.0001$ ). Dexmedetomidine produces effective attenuation of stress induced blood glucose levels by its post synaptic  $\alpha_2$  agonist activity; causing a significant reduction in release of Nor epinephrine (Up to 92% - Kallio et al 1989),<sup>23,24</sup> thereby reducing blood glucose level. Its administration, resulting in lower levels of stress response markers (glucose, cortisol and interleukins) to surgery has been seen in studies by Yacout AG et al 2012, Gupta K et al 2013.<sup>7,8</sup>

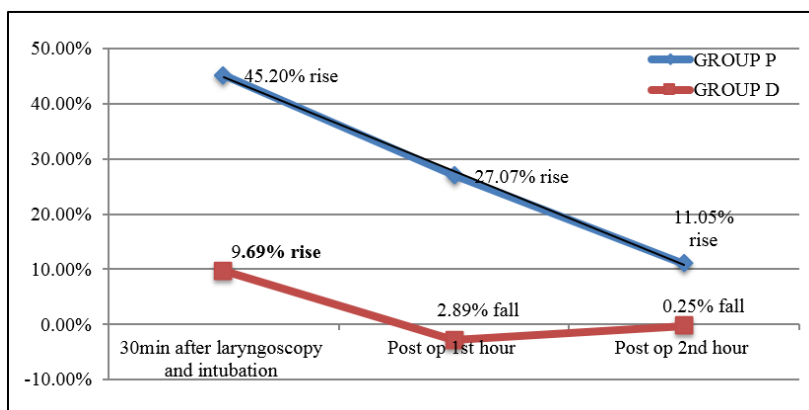


Fig. 5: Percentage wise changes in mean blood glucose levels compared to baseline values



Yacout AG et al 2012<sup>7</sup> demonstrated significant reduction in blood glucose (mg/dl) after recovery and 1<sup>st</sup> day post-operatively in Dexmedetomidine group ( $99.80 \pm 10.78$ ,  $98.27 \pm 11.55$  in Group D versus  $142.07 \pm 14.44$  and  $132.6 \pm 30.25$  in placebo group respectively) ( $p < 0.0001$ ). Harsoor SS et al 2014,<sup>14</sup> in a similar study found significant reduction in blood glucose levels (mg/dl) during 1<sup>st</sup> hour post operatively in Dexmedetomidine group ( $118.2 \pm 16.24$ ) as compared to Placebo group ( $136.95 \pm 19.76$ ) ( $p < 0.0001$ ).

Our study also showed a very highly significant reduction in hourly Sevoflurane consumption during the first and second hour in the Dexmedetomidine group as compared to the normal saline group ( $P < 0.0001$ ) (25.61% and 21.47% in first & second hour respectively). The hypnotic effects of Dexmedetomidine is mediated by the hyperpolarisation of noradrenergic neurons, which suppresses neuronal firing in locus coeruleus along with inhibition of nor epinephrine release and activity in the descending medullospinal noradrenergic pathway.<sup>25</sup> This suppression of inhibitory control triggers neurotransmitters that decrease histamine secretion producing hypnosis similar to normal sleep, without ventilatory depression.<sup>26</sup>

Khan ZP et al 1999<sup>27</sup> showed significant MAC-sparing effects of Dexmedetomidine at plasma concentrations 0.35-0.75 ng/ml. Harsoor SS et al 2014<sup>14</sup> demonstrated 28% reduction in the sevoflurane requirement (ml) in the first hour of anaesthesia ( $15.45 \pm 3.97$  in Group D versus  $11.10 \pm 2.17$  in placebo group). Keniya VM et al 2011 showed 32% reduction in Isoflurane requirement in Group D compared to control group.<sup>22</sup>

The bispectral index (BIS) has previously been shown to be a quantifiable measure of sedative and hypnotic effects of anaesthetics. It analyses both Electroencephalogram (EEG) and Electromyogram (EMG) and displays values ranging 0-100. While numbers towards zero denote very deep anaesthesia, numbers close to 100 indicate that the patient is conscious. Values ranging 40-60 are considered indicative of low probability of consciousness and hence indicative of the adequacy of the depth of anaesthesia. Song et al 1997<sup>28</sup> demonstrated 30 to 38% reduction in the consumption of volatile anaesthetics in BIS-titrated versus control group ( $P < 0.05$ ).

### Bi spectral index monitor



Sevoflurane consumption was measured by Dion's formula in our study. It is a simple routinely usable method, not requiring any special technology for estimation of consumed inhalation agent.<sup>12</sup> This method as compared to Drager's algorithm has been found to underestimate the Sevoflurane consumption by 2.59 ml with limits of agreement between 5.188ml and -0.008ml (Singh PM et al 2013).<sup>13</sup> However, this algorithm is incorporated in Dragger Primus only and not in other lower versions. Dion's technique with slight modification for under estimation could be incorporated electronically in newer anaesthesia machines.<sup>13</sup>

Critical events like laryngoscopy and intubation, pneumoperitoneum caused significant rise in pulse rate, systolic and diastolic blood pressures in Group P in our study, while in Dexmedetomidine group, though there was minimal rise, the values were still significantly lower than baseline ( $p < 0.001$ ). Dexmedetomidine produces its effects on the hemodynamic variables by its  $\alpha$ -2 agonist action on the receptors located in CNS and peripheral smooth muscle cells, leading to a decrease in nor epinephrine release.<sup>23,29</sup>

Kallio A et al 1989, Aantaa R et al 1990 demonstrated a reduction in the nor-epinephrine release upto 92% and 56% respectively with a single intravenous dose of dexmedetomidine.<sup>23,29</sup> Patel CR et al 2013 demonstrated a lesser rise of pulse rate in response to intubation in Dexmedetomidine group (10%) compared to control group (17%).<sup>30</sup> Berrin et al 2007 and Turan et al 2008 have similarly shown the advantageous effects of Dexmedetomidine during intubation and extubation respectively.<sup>31,32</sup>

Hsu YW et al 2004 elicited that Dexmedetomidine, at 0.6-1.2 ng/ml plasma concentration, simulated natural sleep with intact hypercapnic ventilatory response, significant reduction in apnoea-hypopnoea index with intact hypercapnic arousal phenomenon; thereby, changes in  $\text{paCO}_2$  and minute ventilation was found comparable to baseline.<sup>33</sup> Yacout AG et al 2012 assessed recovery profile by measuring tracheal extubation time, time to eye opening and time to following verbal commands which were longer in group D relative to group P but with no statistically significant difference between both groups.<sup>7</sup> Alp Gubert et al 2006 showed tracheal extubation time and 48 hour sedation scores in Dexmedetomidine group (0.5 mcg/kg loading dose, 1mcg/kg/hr maintenance), comparable to placebo group.<sup>9</sup>

Hall JE et al 2000, Carollo DS et al 2008 and Shukry M et al 2010, showed that omitting or halving the loading dose eliminates adverse cardiovascular effects like hypotension, bradycardia but preserves its sedative action.<sup>34-36</sup> Basar et al 2008 and Patel C R et al 2013 have revealed no significant difference in the occurrence of adverse effects between the groups.<sup>30,37</sup>

Other markers of the stress response to anaesthesia and surgery like Interleukin -6 and Nor-epinephrine

could not be measured as facility for these investigations was not available in our institute or even in private labs in the city. Besides, these investigations are quite expensive ones.

### Conclusion

Intravenous Dexmedetomidine given pre and intra operatively serves to be a very useful adjuvant to general anaesthesia by favourably influencing the intra operative stress induced blood glucose levels, sevoflurane requirement and hemodynamic parameters without affecting extubation time, sedation level and incidence of adverse effects.

**Conflicts of Interest:** None.

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