

## Comparative assessment of efficacy of lignocaine (1.5 mg/kg), esmolol (300 µg/kg), and dexmedetomidine (0.5 µg/kg) in minimizing the pressor response to laryngoscopy and intubation

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### ABSTRACT

**Background:** The objectives of the present study were to compare the effect of lignocaine (1.5 mg/kg IV given 3 mins before laryngoscopy and intubation), esmolol (300 µg/kg as a bolus 2 mins before intubation), and dexmedetomidine (0.5 µg/kg IV over 10 mins) on the pressor response in non-hypertensive American Society of Anesthesiologists (ASA) Grade I and II patients posted for elective surgery and the pharmacoeconomic and pharmacoepidemiological inferences drawn on comparison of these drugs.

**Methods:** After approval by the Institutional Ethics Committee, 90 consenting adult patients aged 18-65 years of age of either sex of non-hypertensive ASA Grade I or II undergoing elective surgery under general anesthesia with endotracheal intubation were included in this randomized, prospective study protocol. (1) Group L: Patients were given IV lignocaine 1.5 mg/kg. (2) Group E: Patients were given IV esmolol 300 µg/kg. (3) Group D: Patients were given IV dexmedetomidine 0.5 µg/kg. Adequate monitoring, oxygenation, and hydration were established on the entry in the operating room (OR). All hemodynamic data were measured on arrival in OR, before induction, before intubation, and at 1, 3, 5 mins after intubation by an independent observer. Anesthesia was induced with thiopental sodium and fentanyl 2 µg/kg; intubation was performed with cuffed oral endotracheal tube of appropriate size for airway management. Surgery was allowed to start only after 5 mins of intubation.

**Results:** Esmolol effectively blunted the blood pressure response to intubation, but incompletely attenuated the increase in heart rate (HR). Dexmedetomidine was more effective than lignocaine in minimizing the increase in HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) subsequent to endotracheal intubation.

**Conclusion:** Dexmedetomidine 0.5 µg/kg has manifested to maintain hemodynamic stability associated with intubation and hence may prove beneficial for cardiac patients where the stress response to laryngoscopy and intubation is highly undesirable.

**Keywords:** Dexmedetomidine, Lignocaine, Esmolol, Pharmacoeconomics, Pressor response

### INTRODUCTION

In the 20<sup>th</sup> century, surgery has seen a manifold increase in numbers across the whole world. Laryngoscopy and intubation are obligatory procedures for most patients undergoing surgery under general anesthesia. Despite the advent of new airway devices, rigid laryngoscopy and tracheal intubation are still considered the apogee. However, inevitably it is associated with certain cardiovascular changes such as tachycardia, escalation in blood pressure, and a plethora of cardiac arrhythmias.<sup>1</sup>

The hemodynamic changes stemming from such airway instrumentation are due to sympathoadrenal discharge

caused by epipharyngeal and parapharyngeal stimulations.<sup>2</sup> The sympathetic pressor response to laryngoscopy and intubation can lead to various adverse events like myocardial ischemia, pulmonary edema, acute heart failure, and cerebrovascular accidents, in susceptible individuals.<sup>3-5</sup>

Lignocaine is one of the oldest pharmacological agents to be used for diminishing of the pressor response.<sup>6</sup> Esmolol, an ultra-short acting cardioselective β-blocker with rapid onset when administered intravenously is an attractive option for attenuating this pressor response.<sup>7</sup> α<sub>2</sub> adrenergic agonist dexmedetomidine possesses sympatholytic effects thereby preventing catecholamine release, hypertension, and tachycardia.<sup>8</sup>

During the research process, we have not come across any study which provides a three-drug comparison of lignocaine, esmolol, and dexmedetomidine. Furthermore, dexmedetomidine being a contemporary drug needs further validation and analysis to expedite its applicability. These important reasons prompted us to conduct this study process so as to best evaluate the current standing of this drug with older, yet popular, agents.

### **Objectives**

1. To study and compare the effect of, lignocaine (1.5 mg/kg IV given 3 mins before laryngoscopy and intubation), esmolol (300 µg/kg as a bolus 2 mins before intubation) and dexmedetomidine (0.5 µg/kg IV over 10 mins) on the pressor response in non-hypertensive American Society of Anesthesiologists (ASA) Grade I and II patients posted for elective surgery.
2. Pharmacoeconomic and pharmacoepidemiologic inferences are drawn on comparison of these drugs.

### **METHODS**

After approval by the Institutional Ethics Committee, 90 consenting adult patients aged 18-65 years of age of either sex of non-hypertensive ASA Grade I or II undergoing elective surgery under general anesthesia with endotracheal intubation were included in this randomized, prospective study protocol.

A complete pre-anesthetic check-up of patients was performed prior to their scheduled allotment into the different study groups.

#### **Inclusion criteria**

1. ASA Grade I-II
2. Non hypertensive
3. Either sex
4. 18-65 years age.

#### **Exclusion criteria**

1. History of cardiac and pulmonary disease
2. Pregnancy
3. Morbid obesity
4. Allergy to the study drug
5. Hypertensive patients
6. Impaired kidney or liver function
7. Anticipated difficult airway.

After obtaining written and informed consent, patients were randomly allocated into one of the three groups.

- Group L: Patients were given IV lignocaine 1.5 mg/kg in 10 ml normal saline, 3 mins before laryngoscopy and intubation.

- Group E: Patients were given IV esmolol 300 µg/kg in 10 ml normal saline, 2 mins prior to laryngoscopy and intubation.
- Group D: Patients were given IV dexmedetomidine 0.5 µg/kg over 10 mins as premedication before induction of general anesthesia.

### **Monitoring**

The following parameters were monitored during the intraoperative period:

1. Heart rate (HR)
2. Non-invasive blood pressure (NIBP).

### **Anesthetic technique**

Adequate monitoring, oxygenation, and hydration were established on the entry in the operating room (OR). All hemodynamic data was measured on arrival in OR, before induction, before intubation, and at 1, 3, 5 mins after intubation by an independent observer.

Anesthesia was induced with thiopental sodium and fentanyl 2 µg/kg. After giving injection vecuronium bromide 0.1 mg/kg IV and ventilating the patient with N<sub>2</sub>O and O<sub>2</sub> for 3 mins, intubation was performed with cuffed oral endotracheal tube of appropriate size for airway management.

Surgery was allowed to start only after 5 mins of intubation.

### **Statistical analysis**

Ninety patients were recruited for the study with 30 in each group. The mean and standard deviations of HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in each of the groups were analyzed by analysis of variance (ANOVA) and the paired Student's t-test was commissioned for intragroup analysis. A value of p<0.05 was considered statistically significant.

### **RESULTS**

Demographic characteristics (age, sex) of the three groups were comparable and no statistically significant variance was observed.

Of total 90 patients enrolled in our study, 28 were labeled ASA-I, while the remaining 62 were ASA-II grade.

The values mentioned below corresponded to these instances in time:

1. On arrival in OR
2. Preparatory to induction of anesthesia
3. Post induction and just prior to intubation
4. 1 min post intubation
5. 3 mins post intubation
6. 5 mins post intubation

Intragroup analysis of HR by employing Student's t-test revealed a statistically significant observation for Group L and D ( $p=0.0003$  and  $p=0.0015$ , respectively). On the other hand, intragroup analysis for Group E was statistically insignificant ( $p=2.97$ ). Application of ANOVA for intergroup analysis gives us  $p=0.024$ ,  $F=5.13$ ,  $F_{crit}=3.88$ . The difference between the three means was observed to be statistically significant (Table 1).

Intragroup analyses of SBP by Student's t-test were statistically significant for the three groups L, E and D ( $p=0.001$ ,  $p=0.0002$  and  $p=0.0002$ , respectively). Application of ANOVA gives us  $p=0.022$ ,  $F=5.33$ ,  $F_{crit}=3.88$ . The difference between the three means was observed to be statistically significant (Table 2).

Intragroup analyses of DBP by Student's t-test were statistically significant for the three Groups L, E and D ( $p=0.019$ ,  $P=0.0008$  and  $P=0.0003$ , respectively). Application of ANOVA gives us  $p=0.013$ ,  $F=6.25$ ,  $F_{crit}=3.88$ . The difference between the three means was observed to be statistically significant (Table 3).

From Table 4, we obtain data regarding mean blood pressure (MBP) reduction in three groups, and the average cost of drug per patient. Our analysis shows that dexmedetomidine caused the highest fall in MBP values when compared with lignocaine and esmolol. However, since the unit cost of

dexmedetomidine comes out be Rs 97.65/patient, its cost outweighs the benefits associated with it.

## DISCUSSION

In this study, we have aimed to compare the effect of, lignocaine, esmolol, and dexmedetomidine for diminishing the pressor response. Along with the above parameters one of the defining factors of this study being a detailed review of pharmaco-economic and pharmaco-epidemiologic inferences drawn on comparison of these drugs.

By Table 1, we aim to compare the HR in the three groups at different instances of time. The difference between the 3 means on application of ANOVA was statistically significant, thus highlighting the role of these agents for reducing the HR in response to laryngoscopy and endotracheal intubation. Furthermore, by employing intragroup analysis by Student's t-test, we aimed to study the efficacy of these drugs as standalone agents for reduction in HR.

HR values in Group L show a general decline from HRa to HRf, which is shown to be statistically significant. These findings are in concordance with the studies conducted by Lev and Rosen,<sup>6</sup> Honarmand and Safavi,<sup>9</sup> Splinter and Cervenko,<sup>10</sup> Al-Sabbagh<sup>11</sup> and Malde and Sarode<sup>12</sup> From the results of our study along with the evidence from so many other studies, we can rightfully acknowledge the positive role of intravenous lignocaine for attenuation of HR during laryngoscopy and intubation.

Furthermore, we observed that HR in Group E generally declines from HRa to HRe, but we observe a small increment in values of HRf. This increment in HRf, though slight, on comparison with HRa makes the fall in HR to be statistically non-significant. The result obtained from our study might be an aberration as we see a contrasting result in studies conducted by Zargar et al.,<sup>13</sup> Kindler et al.,<sup>14</sup> Koivusalo et al.<sup>15</sup> and Rathore et al.<sup>1</sup> The variance of our study can be attributed to inadequate dose and the relatively short  $t_{1/2}$  of esmolol.

HR values in Group D show a general decline from HRa to HRf. Comparing all HR values keeping HRa as standard,

**Table 1: Comparison of HRs in three groups at different instances of time.**

Time instance	Mean±SD		
	HR lignocaine	HR esmolol	HR dexmedetomidine
HRa	85.4±2.68	85.86±2.40	84.93±2.61
HRb	82±1.74	81.13±1.94	80.60±2.73
HRc	81.13±1.94	80.73±2.37	78±2.40
HRd	79.53±1.94	80.60±2.73	73.73±2.95
HRe	78±2.40	79.22±3.30	69.93±2.65
HRf	76.66±4.49	79.60±2.31	68.6±3.68

HR: Heart rate, SD: Standard deviation

**Table 2: Comparison of SBP in three groups at different instances of time.**

Time instance	Mean±SD		
	SBP lignocaine	SBP esmolol	SBP dexmedetomidine
SBPa	130.46±4.25	133.86±4.78	138.46±3.09
SBPb	127.80±3.61	131.66±3.89	130.53±2.87
SBPc	122.20±3.25	130.13±3.23	124.06±2.89
SBPd	119.13±2.55	128.80±3.04	121.13±2.50
SBPe	117.20±2.70	127.80±3.61	119.00±2.39
SBPf	115.00±3.66	127.86±3.05	114.00±3.28

SBP: Systolic blood pressure, SD: Standard deviation

**Table 3: Comparison of DBP in three groups at different instances of time.**

Time instance	Mean±SD		
	DBP lignocaine	DBP esmolol	DBP dexmedetomidine
DBPa	79.46±1.96	84.34±2.27	87.00±2.71
DBPb	78.80±1.78	83.20±2.00	80.60±2.73
DBPc	77.44±2.72	81.13±2.01	73.86±3.14
DBPd	74.38±3.00	80.20±2.12	70.86±2.76
DBPe	73.60±3.03	79.46±1.73	68.6±3.11
DBPf	69.60±4.18	79.33±2.24	65.93±3.46

DBP: Diastolic blood pressure

**Table 4: Assessment of cost benefit of three drugs by comparison of fall in MBP versus unit cost.**

Group	SBPa	SBPf	DBPa	DBPf	MBPa	MBPf	Fall in MBP	Unit cost per vial (INR)	Cost for average 70 kg patient
L	130.46	115	79.46	69.6	96.5	84.7	11.8	43	4.51
E	133.86	127.86	84.34	79.33	100.8	95.5	5.3	275	5.77
D	138.46	114	87	65.93	104.2	82	22.2	558	97.65

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure, INR: International normalized ratio

on application of Student’s t-test a value of  $p=0.0015$  is obtained. Thus, confirming the fall in HR to be of statistical significance (Figure 1). This result helps us to establish the efficacy of intravenous dexmedetomidine in attenuating the increase in HR linked to sympathetic overactivity. Our findings confirm the findings established by other authors such as Menda et al.,<sup>16</sup> Bajwa et al.,<sup>17</sup> Isik et al.,<sup>18</sup> Keniya et al.,<sup>19</sup> Kurnik et al.,<sup>20</sup> and Jaakola et al.<sup>21</sup>

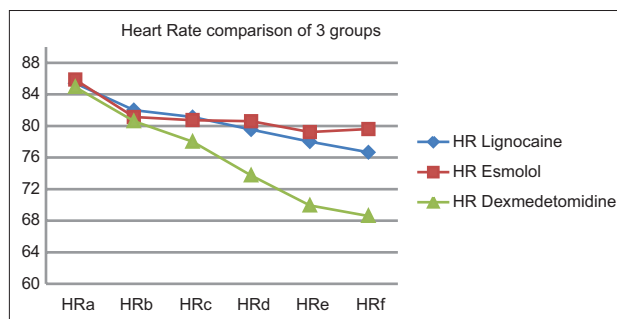
On account of Table 2, we strive to analogize the SBP in the three groups at different instances of time. The difference between the 3 means on application of ANOVA was statistically significant, thus highlighting the role of these agents for reducing the SBP in response to laryngoscopy and endotracheal intubation. From Figure 2, we observe that the fall in SBP in Groups L and D was steeper than that observed in Group E.

SBP values in Group L show a general decline from SBPa to SBPf, which was calculated to be statistically significant. From our obtained results along with results from Lev and Rosen,<sup>6</sup> Honarmand and Safavi,<sup>9</sup> Splinter and Cervenko,<sup>10</sup> Al-Sabbagh<sup>11</sup> and Malde and Sarode,<sup>12</sup> we can affirmatively state that lignocaine 1.5 mg/kg intravenous is helpful in reducing the increase in SBP associated with laryngoscopy and intubation.

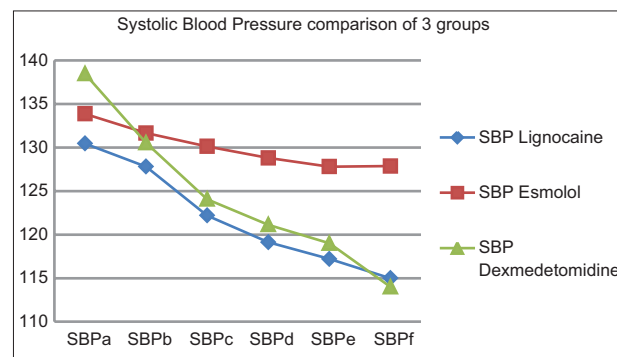
Corresponding values for Group E exhibit an overall decline from SBPa to SBPf, which was deemed to be statistically significant. Our findings bear a striking similarity to results obtained in separate studies conducted by Zargar et al.,<sup>13</sup> Kindler et al.,<sup>14</sup> Koivusalo et al.<sup>15</sup> and Rathore et al.,<sup>1</sup> thus reiterating the efficacy of esmolol for attenuation of SBP after laryngoscopy and endotracheal intubation.

SBP values of Group D were deemed highly significant ( $p=0.0002$ ) on intragroup analysis by Student’s t-test. Studies dealing with intravenous use of dexmedetomidine such as those conducted by Menda et al.,<sup>16</sup> Bajwa et al.,<sup>17</sup> Isik et al.,<sup>18</sup> Keniya et al.,<sup>19</sup> Kurnik et al.<sup>20</sup> and Jaakola et al.,<sup>21</sup> have similarly demonstrated the enhanced efficacy of dexmedetomidine for this purpose.

On account of Table 3, we strive to juxtapose the DBP in the three groups at different instances of time. The difference between the 3 means on application of ANOVA was statistically significant, thus highlighting the role of these agents for reducing the DBP in response to laryngoscopy and endotracheal intubation (Figure 3).



**Figure 1: Comparison of heart rates in three groups at different instances of time.**



**Figure 2: Comparison of systolic blood pressure in three groups at different instances of time.**

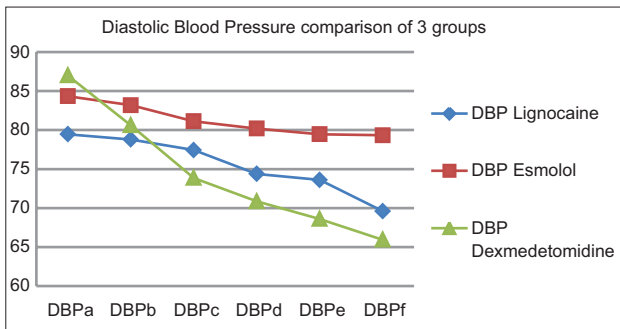
DBP values of Group L show a general decline from DBPa to DBPf which was calculated to be statistically significant. From our obtained results along with results from Lev and Rosen,<sup>6</sup> Honarmand and Safavi,<sup>9</sup> Splinter and Cervenko,<sup>10</sup> Al-Sabbagh<sup>11</sup> and Malde and Sarode<sup>12</sup> we can affirmatively state that lignocaine 1.5 mg/kg intravenous is helpful in reducing the increase in DBP associated with laryngoscopy and intubation.

The DBP values in Group E exhibit an overall decline from DBPa to DBPf, which was deemed to be statistically significant. Our findings bear a striking similarity to results obtained in separate studies conducted by Zargar et al.,<sup>13</sup> Kindler et al.,<sup>14</sup> Koivusalo et al.<sup>15</sup> and Rathore et al.,<sup>1</sup> thus reiterating the efficacy of esmolol for attenuation of DBP after laryngoscopy and endotracheal intubation.

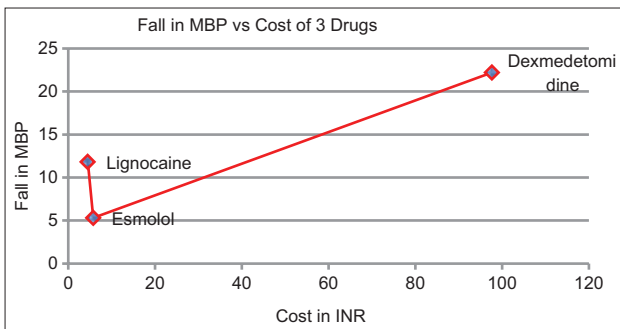
A highly significant p-value (0.0003) was obtained on comparing the fall in SBP in the dexmedetomidine group from DBPa to DBPf. Studies dealing with intravenous use of dexmedetomidine such as those conducted by Menda et al.,<sup>16</sup>

Bajwa et al.,<sup>17</sup> Isik et al.,<sup>18</sup> Keniya et al.,<sup>19</sup> Kurnik et al.,<sup>20</sup> and Jaakola et al.,<sup>21</sup> have similarly demonstrated the enhanced efficacy of dexmedetomidine for this purpose.

Table 4 aims to hold a candle to the pharmacoeconomic and pharmacoepidemiologic inferences of our study by analogizing the assessment of cost-benefit. This was done by comparing the fall in MBP versus the unit cost of the study drugs. The maximum fall in MBP was noted in Group D (22.2 mmHg) while the minimum fall was equated to be in Group E (5.3 mmHg) (Figure 4). However, on comparison keeping the unit cost of the drug in mind the average cost of lignocaine (Rs. 4.51), esmolol (Rs. 5.77), and dexmedetomidine (Rs. 97.65), we ratify that dexmedetomidine was the most expensive drug in our study by a very large margin and lignocaine being the least expensive of the three. This increased cost of dexmedetomidine is a bothersome point in a country like ours where health care is not accessible to all and a majority of the patients are welfare cases. Dexmedetomidine is finding its way into every segment of anesthesia practice and its safety and efficacy as an agent to attenuate the pressor response has been reasonably well established. Thus, keeping in mind, this very important conjecture, we can safely presume that dexmedetomidine is a highly efficacious drug for the attenuation of pressor response to laryngoscopy and endotracheal intubation but is a comparatively expensive proposition even in today's context.



**Figure 3: Comparison of diastolic blood pressure in three groups at different instances of time.**



**Figure 4: Assessment of cost benefit of three drugs by comparison of fall in mean blood pressure versus unit cost.**

## CONCLUSION

We conclude that lignocaine 1.5 mg/kg in 10 ml normal saline 3 mins before laryngoscopy and intubation, esmolol 300 µg/kg in 10 ml normal saline, 2 mins prior to laryngoscopy and intubation, and 0.5 µg/kg dexmedetomidine over 10 mins before induction of anesthesia effectively attenuate the hemodynamic pressor response to laryngoscopy and endotracheal intubation in ASA Grade I and II non-hypertensive patients posted for elective surgery under general anesthesia.

Esmolol 300 µg/kg, 2 mins prior to laryngoscopy and intubation was effective in blunting the blood pressure response to intubation but incompletely attenuated the increase in HR. Further, dexmedetomidine 0.5 µg/kg was more effective than lignocaine 1.5 mg/kg in attenuating the increase in HR, SBP and DBP subsequent to endotracheal intubation.

Dexmedetomidine 0.5 µg/kg has manifested to maintain hemodynamic stability associated with intubation and hence may prove beneficial for cardiac patients where the stress response to laryngoscopy and intubation is highly undesirable. The increased efficacy of dexmedetomidine is also associated with an increased cost associated with the drug. Thus, its use in populations not at risk is currently unwarranted especially in developing economies like India.

In summary dexmedetomidine, a highly selective  $\alpha_2$  adrenoreceptor agonist has many desirable clinical advantages that warrant its employment in the perioperative period.

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