Comparison of the Efficacy of Clonidine and Dexmedetomidine Infusions Administered Preoperatively for Attenuation of the Hemodynamic Response Following Laryngoscopy and Endotracheal Intubation in a Placebo-Controlled Study

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INTRODUCTION
It is well established that laryngoscopy and endotracheal intubation invariably cause haemodynamic changes associated with increased heart rate, increased blood pressure and occasional disturbance in cardiac rhythm. These hemodynamic alterations are hazardous to the patients with hypertension, myocardial insufficiency or cerebrovascular disease. In patients with coronary artery disease it may lead to myocardial ischaemia and dysrhythmia. In hypertensive patients these exaggerated haemodynamic responses may lead to left ventricular failure, pulmonary oedema and congestive cardiac failure.

AIM & OBJECTIVE
In this placebo-controlled, randomized, double-blind, unicentric, prospective study an attempt has been made to observe, assess, and compare the efficacy of preoperative clonidine and dexmedetomidine infusions in attenuating the hemodynamic response following laryngoscopy and endotracheal intubation in three groups of adult patients of either sex undergoing various elective abdominal surgeries under general anaesthesia.

EXCLUSION CRITERIA
Patients with higher Mallampati class (III and IV), Patients on antihypertensive drugs, patients with altered liver functions and renal functions, women of reproductive age group with a history of amenorrhoea and a positive urine test for pregnancy were excluded from study.

MATERIALS AND METHOD
Ninety patients in the age group between 25 and 50 years, of either sex, of ASA physical status I and II, undergoing various elective abdominal surgeries under general anaesthesia were randomly allocated into three equal groups (n=30): Group-C (clonidine), Group-D (dexmedetomidine), and Group-N (normal saline or control). Group-C and Group-D received infusion of clonidine 3 µg kg⁻¹ in normal saline and dexmedetomidine 1 µg kg⁻¹ in normal saline respectively. Group-N (control) received only normal saline infusion. The infusions were given 20 minutes before induction of anaesthesia over a period of 15 minutes. In all patients general
anaesthesia were induced with 2.5% thiopental sodium 4-5 mg kg⁻¹ and neuromuscular blockade with Vecuronium 0.1 mg kg⁻¹ intravenously. Randomization was achieved by closed envelopes chosen by patients prior to the procedure. Subsequently tracheal intubation with an appropriate size endotracheal tube was performed in less than 15 seconds. Anaesthesia was maintained with 66% nitrous oxide in oxygen and Isoflurane 1%. Hemodynamic parameters (HR, SBP, DBP and MAP) were recorded before study drug infusion, after infusion, after induction, during laryngoscopy and intubation, 1, 2, 3, 5 and 10 minutes after intubation. No surgical stimulus was allowed during the study period and hemodynamic changes beyond the study period were not taken into account. At the end of surgery the patients were adequately reversed. In postoperative period the patients were monitored in the recovery room for any complications and appropriately treated if required.

RESULT ANALYSIS
The results of the observations thus obtained in each group of patients were tabulated, compiled and statistically analyzed using Microsoft™ Excel™ 2007 for Mac (version 12.0), StatPlus®:Mac 2009 (version 5.8.3.8) and SPSS version 13.0. Hemodynamic parameters within group at different time intervals were compared with baseline value with repeated measures by ANOVA. A $p$ value < 0.05 was considered as statistically significant and < 0.01 was considered as highly significant.

DEMOGRAPHIC VARIABLES

**Table 1. Comparison of demographic variables between three study groups**

| Demographic Variables | Group C (n =30) Mean ± SD | Group D (n =30) Mean ± SD | Group N (n =30) Mean ± SD | p value |
|-----------------------|---------------------------|---------------------------|---------------------------|---------|
| Sex (M : F)           | 12 : 18                   | 10 : 20                   | 10 : 20                   | 0.8237  |
| Age (years)           | 38.03 ± 8.16              | 39.07 ± 8.39              | 39.13 ± 8.37              | 0.8487  |
| Body weight (kg)      | 56.07 ± 9.68              | 56.90 ± 9.94              | 55.83 ± 9.81              | 0.9029  |
| Height (cm)           | 161.63 ± 9.39             | 160.3 ± 10.39             | 159.63 ± 9.57             | 0.7043  |
| ASA grade (I : II)    | 24 : 6                    | 24 : 6                    | 23 : 7                    | 0.9355  |

SD : standard deviation

All the three groups were statistically comparable with respect to sex, age, body weight, height and ASA grading. No significant differences were observed between the groups ($p$ value > 0.05) [Table 1].

**Table 2. Types of operative procedures in three study groups**

| Operative procedures | Group C (n =30) | Group D (n =30) | Group N (n =30) | Statistical Analysis |
|----------------------|-----------------|-----------------|-----------------|----------------------|
| TAH + BSO            | 5               | 4               | 6               |                     |
| LAVH                 | 3               | 3               | 3               |                     |
| Diagnostic laparoscopy | 2             | 3               | 2               | Chi-Square          |
| Procedure                        | Group C | Group D | Group N | (χ²) value |
|----------------------------------|---------|---------|---------|------------|
| Excision of tubo-ovarian mass    | 1       | 2       | 1       |            |
| Myomectomy                       | 1       | 1       | 2       | 4.6584**   |
| Cholecystectomy                  | 8       | 7       | 8       |            |
| Laparoscopic cholecystectomy     | 5       | 3       | 4       |            |
| Appendectomy                     | 2       | 3       | 2       | 0.9993     |
| Laparoscopic appendicectomy      | 2       | 1       | 1       |            |
| Incisional hernia repair         | 1       | 3       | 1       |            |

TAH + BSO: Trans-abdominal hysterectomy with bilateral salpingo-oophorectomy
LAVH: Laparoscopy assisted vaginal hysterectomy

**HAEMODYNAMIC PARAMETERS**

**HEART RATE**

**Table 3. Comparison of heart rates between and within the study groups at different points of time**

| Time interval                        | Group C (Mean ± SD) | Group D (Mean ± SD) | Group N (Mean ± SD) | p value |
|--------------------------------------|---------------------|---------------------|---------------------|---------|
| Before study drug infusion (baseline) (T1) | 83.13 ± 9.24        | 84.03 ± 9.14        | 83.27 ± 9.49        | 0.9213  |
| After study drug infusion (T2)        | 80.60 ± 8.52        | 79.17 ± 8.66 *      | 83.93 ± 8.79        | 0.0953  |
| After induction of anaesthesia (T3)   | 78.03 ± 8.51 *      | 76.10 ± 8.18 **     | 81.80 ± 8.57        | 0.0320  |
| During laryngoscopy and intubation (T4)| 87.90 ± 6.98 *      | 83.63 ± 6.74        | 98.47 ± 7.77 **     | < 0.0001|
| 1 minute after intubation (T5)        | 93.63 ± 7.06 **     | 87.63 ± 7.55        | 107.67 ± 6.38 **    | < 0.0001|
| 2 minutes after intubation (T6)       | 91.43 ± 7.09 **     | 86.07 ± 7.32        | 103.13 ± 6.76 **    | < 0.0001|
| 3 minutes after intubation (T7)       | 84.50 ± 7.29        | 81.83 ± 6.72        | 94.70 ± 8.41 **     | < 0.0001|
| 5 minutes after intubation (T8)       | 80.27 ± 6.48        | 78.00 ± 6.95 **     | 86.63 ± 6.63        | < 0.0001|
| 10 minutes after intubation (T9)      | 77.17 ± 6.69 **     | 76.83 ± 7.03 **     | 81.50 ± 7.48        | 0.0200  |

SD: standard deviation
Statistically significant (p < 0.05) [when compared with baseline value within group]
Statistically highly significant (p < 0.01) [when compared with baseline value within group]
COMPARISON BETWEEN GROUPS
When the preoperative baseline HR was compared between three groups, no statistically significant difference was found (p value 0.9213). HR was also similar in all groups after study drug infusion (p value 0.0953). After induction of anaesthesia, a significant reduction in HR was noted in Group D (p value 0.032). The increases in HR during laryngoscopy and intubation, at 1, 2, 3 and 5 minutes after intubation were highly significant in Group N compared to Group C and Group D (p value < 0.01). After 10 minutes of intubation, it was also significant in Group N (p value 0.02) [Table 3].

COMPARISON WITHIN GROUP
Group C: The change in HR after study drug infusion was not statistically significant (p value 0.274). But, a significant fall in HR was observed after induction of anaesthesia (p value 0.03). HR increased significantly during laryngoscopy and intubation (p value 0.0279). Highly significant rise in HR occurred at 1 and 2 minutes after intubation (p value < 0.01). Thereafter, HR decreased gradually and remained around the baseline value. No significant difference was observed at 3 and 5 minutes after intubation (p value 0.5271 and 0.1693 respectively). After 10 minutes of intubation, HR decreased further and became highly significant (p value < 0.01).

Group D: HR decreased significantly after study drug infusion compared to the baseline value (p value 0.0385). A highly significant fall in HR occurred after induction of anaesthesia (p value < 0.01). HR remained around the baseline value during laryngoscopy and intubation, at 1, 2 and 3 minutes after intubation and no significant difference was observed (p value > 0.05). Thereafter, HR decreased again from the baseline value and became highly significant at 5 and 10 minutes after intubation (p value < 0.01).

Group N: When compared with the baseline HR, no significant difference was noted after study drug infusion (p value 0.7788) and induction of anaesthesia (p value 0.5324). HR increased and remained persistently high during laryngoscopy and intubation, at 1, 2 and 3 minutes after intubation. Statistically highly significant values were noted throughout this period (p value < 0.01). Thereafter, HR decreased gradually and remained around the baseline value. No significant difference was observed at 5 and 10 minutes after intubation (p value 0.1166 and 0.4266 respectively).

SYSTOLIC BLOOD PRESSURE
Table 4. Comparison of systolic blood pressures between and within the study groups at different points of time

| Time interval                            | SYSTOLIC BLOOD PRESSURE (mm of Hg) | p value |
|------------------------------------------|------------------------------------|---------|
|                                          | Group C (n =30) (Mean ± SD)        |         |
|                                          | Group D (n =30) (Mean ± SD)        |         |
|                                          | Group N (n =30) (Mean ± SD)        |         |
| Before study drug infusion (baseline) (T1)| 121.60 ± 11.76  | 122.47 ± 12.22  | 120.63 ± 12.37  | 0.8433 |
| After study drug infusion (T2)           | 115.77 ± 10.93  | 109.70 ± 11.97 **| 118.57 ± 11.12  | 0.0104 |
| After induction of anaesthesia (T3)      | 106.87 ± 10.76 **| 101.33 ± 10.96 **| 112.83 ± 11.37 *| < 0.0001 |
| During laryngoscopy and intubation (T4)  | 123.33 ± 9.69  | 118.77 ± 8.15  | 137.60 ± 8.05 **| < 0.0001 |
| 1 minute after                           | 130.77 ± 8.11 **| 123.50 ± 9.10  | 148.00 ± 7.60 **| < 0.0001 |
intubation (T5) & 127.47 ± 8.69 * & 122.53 ± 8.02 & 142.47 ± 7.52 ** & < 0.0001 \\
intubation (T6) & 117.67 ± 9.66 & 113.73 ± 8.51 ** & 130.23 ± 7.97 ** & < 0.0001 \\
intubation (T7) & 110.53 ± 9.84 ** & 110.30 ± 8.66 ** & 119.97 ± 7.87 & < 0.0001 \\
intubation (T8) & 107.73 ± 9.36 ** & 109.07 ± 8.85 ** & 113.47 ± 8.44 * & 0.0363 \\
intubation (T9) & SD : standard deviation \\

Statistically significant ($p < 0.05$) [when compared with baseline value within group]
Statistically highly significant ($p < 0.01$) [when compared with baseline value within group]

COMPARISON BETWEEN GROUPS

When the preoperative baseline SBP was compared between three groups, no statistically significant difference was found ($p$ value 0.8433). After study drug infusion, a significant reduction in SBP was noted in Group D ($p$ value 0.0104). After induction of anaesthesia, this reduction in SBP became highly significant in Group D ($p$ value < 0.01). The increases in SBP during laryngoscopy and intubation, at 1, 2, 3 and 5 minutes after intubation were highly significant in Group N compared to Group C and Group D ($p$ value < 0.01). After 10 minutes of intubation, it was also significant in Group N ($p$ value 0.0363) [Table 4].

COMPARISON WITHIN GROUP

Group C: The change in SBP after study drug infusion was not statistically significant ($p$ value 0.0514). But, a highly significant fall in SBP was observed after induction of anaesthesia ($p$ value < 0.01). SBP increased during laryngoscopy and intubation but it was statistically insignificant ($p$ value 0.5358). The increase in SBP was highly significant at 1 minute after intubation ($p$ value < 0.01) and significant at 2 minutes after intubation ($p$ value 0.032). Thereafter, SBP decreased near the baseline value and no significant difference was observed at 3 minutes after intubation ($p$ value 0.1623). At 5 and 10 minutes after intubation, SBP decreased further and became highly significant ($p$ value < 0.01).

Group D: SBP decreased from the baseline value after study drug infusion and induction of anaesthesia, which was highly significant ($p$ value < 0.01). SBP remained around the baseline value during laryngoscopy and intubation, at 1 and 2 minutes after intubation and no significant difference was observed ($p$ value > 0.05). Thereafter, SBP decreased again from the baseline value and became highly significant at 3, 5 and 10 minutes after intubation ($p$ value < 0.01).

Group N: When compared with the baseline SBP, no significant difference was noted after study drug infusion ($p$ value 0.4988). A significant fall in SBP occurred after induction of anaesthesia ($p$ value 0.0137). SBP increased and remained persistently high during laryngoscopy and intubation, at 1, 2 and 3 minutes after intubation. Statistically highly significant values were noted throughout this period ($p$ value < 0.01). Thereafter, SBP decreased near the baseline value and no significant difference was observed at 5 minutes after intubation ($p$ value 0.8041). At 10 minutes after intubation, SBP decreased significantly from the baseline value ($p$ value < 0.0111).
### DIASTOLIC BLOOD PRESSURE

**Table 5.** Comparison of diastolic blood pressures between and within the study groups at different points of time

| Time interval | DIASTOLIC BLOOD PRESSURE (mm of Hg) | p value |
|---------------|------------------------------------|---------|
|               | Group C (n =30) (Mean ± SD) | Group D (n =30) (Mean ± SD) | Group N (n =30) (Mean ± SD) |
| Before study drug infusion (baseline) (T1) | 80.83 ± 9.44 | 79.73 ± 9.47 | 79.27 ± 9.67 | 0.8082 |
| After study drug infusion (T2) | 75.67 ± 9.09 * | 72.10 ± 8.25 ** | 78.00 ± 9.17 | 0.0374 |
| After induction of anaesthesia (T3) | 69.97 ± 8.36 ** | 67.67 ± 7.69 ** | 73.53 ± 9.46 * | 0.0307 |
| During laryngoscopy and intubation (T4) | 82.60 ± 9.07 | 78.37 ± 7.42 | 87.83 ± 6.65 ** | < 0.0001 |
| 1 minute after intubation (T5) | 86.37 ± 9.21 * | 81.83 ± 7.55 | 95.87 ± 7.21 ** | < 0.0001 |
| 2 minutes after intubation (T6) | 85.00 ± 8.88 | 80.47 ± 7.15 | 92.33 ± 6.79 ** | < 0.0001 |
| 3 minutes after intubation (T7) | 78.67 ± 9.30 | 75.93 ± 7.58 | 83.47 ± 7.21 | 0.0019 |
| 5 minutes after intubation (T8) | 74.17 ± 9.24 ** | 73.13 ± 7.41 ** | 78.83 ± 6.52 | 0.0129 |
| 10 minutes after intubation (T9) | 71.20 ± 9.08 ** | 72.37 ± 7.88 ** | 73.23 ± 7.27 ** | 0.6217 |

SD: standard deviation  
Statistically significant (p< 0.05) [when compared with baseline value within group]  
Statistically highly significant (p< 0.01) [when compared with baseline value within group]

#### COMPARISON BETWEEN GROUPS

When the preoperative baseline DBP was compared between three groups, no statistically significant difference was found (p value 0.8082). Significant reductions in DBP were noted in Group D after study drug infusion (p value 0.0374) and after induction of anaesthesia (p value 0.0307). The increases in DBP during laryngoscopy and intubation, at 1, 2, and 3 minutes after intubation were highly significant in Group N compared to Group C and Group D (p value < 0.01). After 5 minutes of intubation, it was also significant in Group N (p value 0.0129). DBP became similar in all groups after 10 minutes of intubation (p value 0.6217) [Table 5].

#### COMPARISON WITHIN GROUP

Group C: DBP decreased from the baseline value initially, which was statistically significant after study drug infusion (p value 0.0349) and highly significant after induction of anaesthesia (p value < 0.01). DBP increased during laryngoscopy and intubation but it was statistically insignificant (p value 0.4626). The increase in DBP was statistically significant at 1 minute after intubation (p value 0.0251). Thereafter, DBP decreased gradually and remained around the baseline value. No significant difference was observed at 2 and 3 minutes after intubation (p value 0.0835 and 0.3741 respectively). At 5 and 10 minutes after intubation, DBP became similar in all groups (p value 0.6217).
intubation, DBP decreased further and became highly significant \( (p \text{ value} < 0.01) \).

Group D: DBP decreased from the baseline value after study drug infusion and induction of anaesthesia, which was highly significant \( (p \text{ value} < 0.01) \). DBP remained around the baseline value during laryngoscopy and intubation, at 1, 2 and 3 minutes after intubation and no significant difference was observed \( (p \text{ value} > 0.05) \). Thereafter, DBP decreased again from the baseline value and became highly significant at 5 and 10 minutes after intubation \( (p \text{ value} < 0.01) \).

Group N: When compared with the baseline DBP, no significant difference was noted after study drug infusion \( (p \text{ value} 0.6045) \). A significant fall in DBP occurred after induction of anaesthesia \( (p \text{ value} 0.0238) \). DBP increased and remained persistently high during laryngoscopy and intubation, at 1 and 2 minutes after intubation. Statistically highly significant values were noted throughout this period \( (p \text{ value} < 0.01) \). Thereafter, DBP decreased gradually and remained around the baseline value. No significant difference was observed at 3 and 5 minutes after intubation \( (p \text{ value} 0.0615 \text{ and } 0.8394 \text{ respectively}) \). At 10 minutes after intubation, DBP decreased further and became highly significant \( (p \text{ value} < 0.01) \).

**MEAN ARTERIAL PRESSURE**

Table 6. Comparison of mean arterial pressures between and within the study groups at different points of time

| Time interval                  | MEAN ARTERIAL PRESSURE (mm of Hg) | \( p \text{ value} \) |
|-------------------------------|----------------------------------|------------------------|
|                               | Group C \( (n =30) \)             | Group D \( (n =30) \)  | Group N \( (n =30) \)  |
|                               | (Mean ± SD)                       | (Mean ± SD)            | (Mean ± SD)            |
| Before study drug infusion    | 94.33 ± 10.19                     | 93.90 ± 10.33          | 93.07 ± 10.57          | 0.8923 |
| infusion (baseline) (T1)     |                                  |                       |                       |
| After study drug infusion     | 89.07 ± 9.59 \*                  | 84.70 ± 9.41 \*       | 91.43 ± 9.66          | 0.0246 |
| (T2)                          |                                  |                       |                       |
| After induction of anaesthesia| 82.03 ± 9.14 \*                  | 78.90 ± 8.68 \*       | 86.67 ± 10.09 \*      | 0.0069 |
| (T3)                          |                                  |                       |                       |
| During laryngoscopy and intubation | 96.10 ± 9.11                 | 91.83 ± 7.49          | 104.47 ± 6.88 \*      | < 0.0001 |
| (T4)                          |                                  |                       |                       |
| 1 minute after intubation     | 101.13 ± 8.51 \*                 | 95.80 ± 7.91          | 113.20 ± 7.18 \*      | < 0.0001 |
| (T5)                          |                                  |                       |                       |
| 2 minutes after intubation    | 99.23 ± 8.63 \*                  | 94.50 ± 7.33          | 109.07 ± 6.81 \*      | < 0.0001 |
| (T6)                          |                                  |                       |                       |
| 3 minutes after intubation    | 91.73 ± 9.25                     | 88.57 ± 7.61 \*       | 99.00 ± 7.33 \*       | < 0.0001 |
| (T7)                          |                                  |                       |                       |
| 5 minutes after intubation    | 86.30 ± 9.21 \*                  | 85.50 ± 7.51          | 92.50 ± 6.80          | 0.0014 |
| (T8)                          |                                  |                       |                       |
| 10 minutes after intubation   | 83.37 ± 8.98 \*                  | 84.60 ± 7.93          | 86.63 ± 7.58 \*       | 0.2971 |
| (T9)                          |                                  |                       |                       |

SD : standard deviation
Statistically significant \( (p< 0.05) \) [when compared with baseline value within group]
Statistically highly significant \( (p< 0.01) \) [when compared with baseline value within group]
COMPARISON BETWEEN GROUPS
When the preoperative baseline MAP was compared between three groups, no statistically significant difference was found \((p\text{ value } 0.8923)\). After study drug infusion, a significant reduction in MAP was noted in Group D \((p\text{ value } 0.0246)\). After induction of anaesthesia, this reduction in MAP became highly significant in Group D \((p\text{ value } < 0.0069)\). The increases in MAP during laryngoscopy and intubation, at 1, 2, 3 and 5 minutes after intubation were highly significant in Group N compared to Group C and Group D \((p\text{ value } < 0.01)\). MAP became similar in all groups after 10 minutes of intubation \((p\text{ value } 0.2971)\) [Table 6].

COMPARISON WITHIN GROUP
Group C: MAP decreased from the baseline value initially, which was statistically significant after study drug infusion \((p\text{ value } 0.0437)\) and highly significant after induction of anaesthesia \((p\text{ value } < 0.01)\). MAP increased during laryngoscopy and intubation but it was statistically insignificant \((p\text{ value } 0.4816)\). The increase in MAP was highly significant at 1 minute after intubation \((p\text{ value } < 0.01)\) and significant at 2 minutes after intubation \((p\text{ value } 0.049)\) Therereafter, MAP decreased near the baseline value and no significant difference was observed at 3 minutes after intubation \((p\text{ value } 0.3051)\). At 5 and 10 minutes after intubation, MAP decreased further and became highly significant \((p\text{ value } < 0.01)\).

Group D: MAP decreased from the baseline value after study drug infusion and induction of anaesthesia, which was highly significant \((p\text{ value } < 0.01)\). MAP remained around the baseline value during laryngoscopy and intubation, at 1 and 2 minutes after intubation and no significant difference was observed \((p\text{ value } > 0.05)\). Thereafter, MAP decreased again from the baseline value and became significant at 3 minutes after intubation \((p\text{ value } 0.0265)\) and highly significant at 5 and 10 minutes after intubation \((p\text{ value } < 0.01)\).

Group N: When compared with the baseline MAP, no significant difference was noted after study drug infusion \((p\text{ value } 0.5345)\). A significant fall in MAP occurred after induction of anaesthesia \((p\text{ value } 0.0197)\). MAP increased and remained persistently high during laryngoscopy and intubation.

CONCLUSION
From these observations and analysis of the present study, it can be inferred that both clonidine and dexmedetomidine administered intravenously just before laryngoscopy and endotracheal intubation effectively attenuated the hemodynamic response by limiting the extent of rises in heart rate and blood pressure. Dexmedetomidine has been found to provide better hemodynamic stability than clonidine. Both the $\alpha_2$-agonists are devoid of any serious adverse effect and found safe in this study.

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