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*Original Research Article*

# Evaluation of Synergistic and Co-induction Effects of Propofol and Midazolam: An Institutional Based Study

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## ABSTRACT

**Background:** Auto-co-induction is a technique of giving a pre-calculated dose of induction agent prior to giving the full dose of same induction agent; this technique is also known as "the priming technique". Co-induction is defined as the concurrent administration of two or more drugs that facilitate induction of anaesthesia documenting synergism. Propofol and midazolam is a commonly used combination for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression.

**Materials & Methods:** The present study was conducted in Department of Anaesthesiology, CCM Medical College, Kachandur, Durg, Chhattisgarh (India) after obtaining the approval of Institutional Ethical Committee. Ninety patients of age between 18 and 65 years, American Society of Anesthesiologist (ASA) Grade I and II, from both sexes having no history of adverse anaesthetic reaction, were randomly allocated into three equal groups: group SP (saline-propofol), group MP (midazolam-propofol) and group PP (propofol-propofol), consisting of 30 patients in each. Group SP received 10 ml of normal saline followed by 0.5 mg/kg propofol IV, group MP received 0.03 mg/kg IV midazolam followed by 0.5 mg/kg propofol IV and group PP received 0.5 mi/kg of propofol followed by 0.5 mg/kg propofol IV till adequate jaw relaxation achieved.

**Results & Conclusions:** The present study compared the efficacy of propofol auto-co-induction versus midazolam propofol co-induction. A significant fall in the induction dose requirement of propofol is found in both the study groups. The priming in relation to propofol provides haemodynamic stability both at post-induction interval and secondary to intubation. However, more studies with larger samples are required before considering these observations as generalised.

**Keywords: Synergism,** Co-induction Effect, Propofol, Midazolam.

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## INTRODUCTION

"Auto-co-induction" is a technique of giving a pre-calculated dose of induction agent prior to giving the full dose of same induction agent; this technique is also known as "the priming technique".[1-3] Application of priming principle is well documented in relation to the use of muscle relaxants.

"Co-induction" is defined as the concurrent administration of two or more drugs that facilitate induction of anaesthesia documenting synergism.[4-7]

However, there is a paucity of studies documenting the application of priming principle in induction agents. This technique, in relation to induction agents, aims at utilising the sedative, anxiolytic and amnesic properties at sub-hypnotic dosage of induction agent when given a few minutes prior to induction. This study was also done to evaluate whether the priming technique reduces the effective dose of induction agent and favourably influences the peri-intubation haemodynamics. Propofol and midazolam is a commonly used combination for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression.

## MATERIALS AND METHODS

The present study was conducted in Department of Anaesthesiology, CCM Medical College, Kachandur, Durg, Chhattisgarh (India) after obtaining the approval of Institutional Ethical Committee.

Ninety patients of age between 18 and 65 years, American Society of Anesthesiologist (ASA) Grade I and II, from both sexes having no history of adverse anaesthetic reaction, were randomly allocated into three equal groups: group SP (saline-propofol), group MP (midazolam-propofol) and group PP (propofol-propofol), consisting of 30 patients in each.

In the operation theatre, baseline heart rate (HR), $Spo_2$, non-invasive systolic blood pressure (SBP). Intravenous cannula was inserted. The patients were preloaded with 10 ml/kg of crystalloids. Using computers generalized data, the patients were randomly allocated to one of the three groups. Depending on the group, the following methods of induction were used-

Group SP received 10 ml of normal saline followed by 0.5 mg/kg propofol IV till adequate jaw relaxation achieved, group MP received 0.03 mg/kg IV midazolam followed by 0.5 mg/kg propofol IV till adequate jaw relaxation achieved and group PP received 0.5 mi/kg of propofol followed by 0.5 mg/kg propofol IV till adequate jaw relaxation achieved. LMA was inserted after adequate jaw relaxation was achieved, using the insertion technique as described by Brain [82]. Another bolus of propofol 0.5 mg $kg^{-1}$ was given if the patient had airway reflexes preventing LMA insertion or limb and head movement coming restraint. Another attempt at LMA insertion was made after 30 seconds and the cycle repeated till the LMA was successfully inserted and the patient did not have coughing, swallowing or gagging.

The position of LMA was checked by observing chest movement, auscultation of chest during gentle IPPV and capnography and anaesthesia was continued as per the requirement of the surgery.

**Parameters**

1. HR and SBP were monitored throughout the procedure and recorded at 1- minute intervals starting just before induction until LMA was in place.
2. Assessment of conditions related to induction/co-induction/auto-co- induction was done using following criteria
   A. Time taken for induction
   B. Ease of LMA insertion at the first attempt and number of attempts required to insert LMA successfully without the patient having any airway reflexes, were recorded.

Ease of LMA insertion at first attempt was graded according to a three point scale.

Grade 1: Excellent, no response to LMA insertion
Grade 2: Acceptable, gagging, swallowing or coughing
Grade 3: Poor, unable to open mouth or biting

3. Consumption of Propofol/Midazolam per patient

**Statistical Analysis**

Statistical analysis was done by using descriptive and inferential statistics using Chi square test and Student's unpaired t test. The software used in the analysis were SPSS 17.0 version and GraphPad Prism 5.0 and $p<0.05$ is considered as level of significance ($p<0.05$).

**Table 1: Demographic Profile**

| | Group SP | | Group MP | | Group PP | |
|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** |
| **Age(yrs)** | 33.90 | 12.51 | 41.13 | 13.58 | 39.43 | 11.94 |
| **Weight(kg)** | 57.96 | 9.28 | 52.46 | 10.97 | 54.16 | 10.36 |
| **Male** | 18(60%) | | 18(60%) | | 6(20%) | |
| **Female** | 12(40%) | | 12(40%) | | 24(80%) | |
| **Type of surgeries** | | | | | | |
| General surgery | 14(46.67%) | | 14(46.67%) | | 13(43.33%) | |
| Orthopedic | 3(10%) | | 2(6.67%) | | 5(16.67%) | |
| Gynecology | 11(36.67%) | | 12(40%) | | 8(26.67%) | |
| Otorhinology | 2(6.67%) | | 2(6.67%) | | 4(13.33%) | |
| **ASA Grading** | | | | | | |
| I | 29(96.67%) | | 14(46.67%) | | 29(96.67%) | |
| II | 1(3.33%) | | 16(53.33%) | | 1(3.33%) | |

**Table 2: Total dose of Propofol required for induction and induction time in three groups**

| | **Group SP** | **Group MP** | **SP:MP** |
|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | **Significance** |
| **Mean total induction dose of propofol(mg)** | 166.83±4.10 | 96.11±22.54 | p=0.045 (S) |
| **Induction Time(second) or jaw relaxation time** | 171.33±34.61 | 105.00±23.30 | p=0.000 (S) |
| | **Group SP** | **Group PP** | **SP:PP** |
| **Mean total induction dose of propofol(mg)** | 166.83±4.10 | 100.33±24.45 | p=0.009 (S) |
| **Induction Time(second) or jaw relaxation time** | 171.33±34.61 | 115.00±23.74 | p=0.000 (S) |
| | **Group MP** | **Group PP** | **MP:PP** |
| **Mean total induction dose of propofol(mg)** | 96.11±22.54 | 100.33±24.45 | P=0.687 (NS) |
| **Induction Time(second) or jaw relaxation time** | 105.00±23.30 | 115.00±23.74 | P=0.347(NS) |

## RESULTS AND DISCUSSION

When propofol and midazolam are combined they act synergistically.[5] The arguments for co-induction are two-fold to improve the balance of desired versus adverse effects.[5] When used in this way midazolam has been shown to reduce the dose of propofol required to induce anaesthesia by up to 50% without affecting the recovery profile

A drug may augment its own effects "auto-co-induction". Repeated dosing using the same drug may elicit different responses with successive doses. Recently studies have been conducted comparing intravenous propofol-propofol auto-co induction as an alternative to propofol-midazolam co-induction for induction of anaesthesia.[5] In one of these studies these two co-induction techniques have shown less decrease in mean arterial pressure during induction, a significant reduction of total induction dose of propofol and a decreased incidence of apnoea during induction of anaesthesia, while in the other study the decrease in systolic blood pressure following induction was significantly greater in the propofol auto-co-induction group and a significant reduction of the dose of propofol required to induce anaesthesia in the midazolam-propofol co-induction and propofol auto-co-induction group was recorded.[5]

In view of these observations of earlier workers and because of dearth of data in this regard, we undertook the present study. Ninety patients were selected for the study and divided into three groups that were demographically comparable.

As seen in graph 1 mean baseline HR taken just before giving intravenous saline was 103.00 ± 18.56 bpm. Post-induction the heart rate decreased to 100.23 ± 12.09 bpm at 120 sec. which was statistically significant ($p<0.05$).This decrease in heart rate can be attributed to the vagotonic properties of propofol. The baroreflex mediated increase in heart rate, which is associated with hypotensive response, seen with other intravenous induction agents is not seen with propofol[5].

As seen in graph 2 mean baseline SBP was 134.5 ± 14.99 mmHg. At pre-induction (T-0), the SBP decreased significantly from the baseline ($p <0.05$) at 0 seconds and continued to decrease further till 60 seconds when it was 131.43 ± 11.18 i.e. significantly decreased ($P< 0.05$) from the baseline. We would like to attribute this significant fall in SBP at 0 sec to placebo effect of saline that was given 2 minutes prior to induction as other hemodynamic parameters also indicate this. The further decrease in SBP at 60 sec after induction can be attributed to propofol which causes vasodilatation and a fall in cardiac output.

As seen in Table-2 the mean total dose of propofol required for induction was 166.83 ± 4.1 mg and mean induction time was 171.33 ± 34.61 seconds in this group.

## CONCLUSIONS

The present study compared the efficacy of propofol auto-co-induction versus midazolam propofol co-induction. The following conclusions and inferences can be drawn from this study:

1. A significant fall in the induction dose requirement of propofol is found in both the study groups.
2. The priming in relation to propofol provides haemodynamic stability both at post-induction interval and secondary to intubation.
3. However, more studies with larger samples are required before considering these observations as generalised.

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