Effect of Midazolam Premedication on the Dose of Propofol for Laryngeal Mask Airway Insertion in Children

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ABSTRACT

Background: The present study was conducted on 120 pediatric patients of ASA Grade I and II of either sex aged 3-12 years scheduled for pediatric surgeries under general anaesthesia.

Patients & Methods: All patients were randomly divided into Group A and Group B. Group A was further divided into 3 subgroups of unpremedicated patients who received 3, 4 and 5 mg kg⁻¹ propofol only designated as A1, A2 and A3 respectively. Group B was further divided into subgroups of premedicated patients with midazolam (0.05 mg kg⁻¹) intravenous and received 3, 4 and 5 mg kg⁻¹ propofol designated as B1, B2 and B3 respectively.

Results: Results showed that increasing dose of propofol decreases the adverse events like inadequate jaw relaxation, limb movements, coughing, gagging and laryngospasm. Midazolam when added to propofol further reduces the incidence of adverse events and provides more favorable environment for insertion of LMA. At higher doses of propofol (5 mg kg⁻¹), hypotension is a major problem due to its cardiovascular depressant action. Therefore, 4 mg kg⁻¹ propofol along with midazolam is the optimum dose because there is more hemodynamic stability and we get better conditions for LMA insertion.

Conclusion: Midazolam is an effective premedication in children which is synergistic with propofol and reduces its effective dose, required for LMA insertion.

KEYWORDS: Anaesthesia, Laryngeal mask airway, Laryngospasm, Propofol, Midazolam.

The laryngeal mask airway¹, ² (LMA) has proved to be a popular addition to the range of equipment available for airway management. It appears to be relatively simple and safe to use across a wide range of surgical specialties³. Insertion of LMA is accompanied by lesser cardiovascular responses than those after laryngoscopy and intubation⁴.

Use of LMA in children is becoming increasingly common. Propofol depresses airway reflexes more than thiopentone⁵ and has been shown to be superior to thiopental when these agents were used alone for insertion of LMA so it has been recommended as an induction agent of choice for insertion⁶. The larger central compartment volume is consistent with higher induction dose requirement in children.⁶,⁷ Midazolam is an effective sedative premedicant⁸ in children which is synergistic with propofol⁹ and may reduce dose required for LMA insertion. The aim of the study was to determine the effect of midazolam premedication on the different doses of propofol to find out the optimum dose of propofol for LMA insertion in children and to observe any haemodynamic changes before, during and after insertion of LMA.

PATIENTS AND METHOD

With the approval of the ethical committee of the University, this randomized prospective study was conducted on 120 children one year duration, ASA grade I and II, aged (3-12 years), admitted in various wards of our hospital and Associated Hospitals, scheduled to undergo pediatric surgeries. Informed written consent was taken from parents of each patient. Patients suffering from cardiac abnormalities, neuromuscular disease, pulmonary abnormalities (e.g. asthma), abnormal airway anatomy, any condition with increased risk of regurgitation of gastric contents and prolonged surgeries (>3 hr) were excluded.

Before surgery all patients were randomly assigned to one of two groups:

Group A included three groups of 20 patients each, unpremedicated, who received propofol in doses of 3 mg kg⁻¹ (Gr A1), 4 mg kg⁻¹ (Gr A2) and 5 mg kg⁻¹ (Gr A3) respectively.

Group B included three groups of 20 patients each, premedicated with midazolam (0.05 mg kg⁻¹) and received propofol in doses of 3 mg kg⁻¹, (Gr B1), 4 mg kg⁻¹ (Gr B2) and 5 mg kg⁻¹ (Gr B3) respectively.

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In the operating room, intravenous access was established and, monitors like pulse oximeter, electrocardiogram, ETCO2 and non-invasive blood pressure were applied. In group B, i.v. midazolam (0.05 mg kg⁻¹) was given 10 min before propofol induction. Midazolam has an onset of action of less than 15 minutes. It was assumed that the onset of action of midazolam should have initiated at the time of propofol induction. Injection lignocaine 10 mg was added to each 100 mg propofol. Intravenous propofol was administered over a period of 15 sec, following which lungs were ventilated with 100% oxygen for 60 sec before attempting insertion of LMA. Insertion of LMA was performed by the same grade of people in all the six groups under study.

Observation of mean arterial pressure and heart rate was done before insertion, just after insertion, at 5 and 10 minutes post insertion. All patients were also assessed for following adverse events:-

a) Inadequate relaxation of Jaw.
b) Coughing, gagging, swallowing or laryngospasm.
c) Limb movement.

For analysis of data, chi-square test and for parametric data including multiple comparisons Analysis of Variance (ANOVA) was performed. The present study was conducted as a pilot study, the duration of study was one year only and to get the unbiased results, the demographic matching was necessary. Hence, a sample size of 120 patients to get the preliminary trends was found to be feasible.

RESULTS

Patients undergoing surgery were randomly allocated to different subgroups. The patient characteristics like age, height, sex and weight were comparable. (Table 1)

The type of surgeries which were maximally conducted in all the subgroups were hernia and hypospadias. The miscellaneous surgeries included urethroplasty, anoplasty, biopsies, orthopaedic limb surgeries, corneal perforation.

Incidence of inadequate jaw relaxation was maximum in subgroup A1 (50%), followed by 30% and 20% in subgroup A2 and A3. No such incidence was seen in subgroup B3 while subgroup B1 and B2 showed 20% and 5% respectively. During comparison of subgroups A1 vs B1, A2 vs B2 and A3 vs B3, incidence of inadequate jaw relaxation was significantly decreased (p<0.05) in midazolam-propofol group i.e Group B (Table 2).

Similarly, the lowest incidence of coughing was found in subgroup B3 (5%) while the highest incidence in subgroup A1 (90%). Comparison of subgroup A1 vs B1 and A2 vs B2 showed that the incidence of coughing was significantly higher in A1 and A2 group with p value <0.05. Gagging in subgroup A1 and A2 was significantly high (p<0.05) when compared with subgroup B1 and B2 respectively, but the comparison between A3 and B3 was not significant (p=0.32). Limb movements also had similar trend, with minimum incidence in propofol-midazolam group B (Table 2). No incidence of laryngospasm was seen in any of the groups. Thus, the best condition for insertion of LMA was observed in subgroup A3 among group A (60% successful placement) and in B3 among group B (100% success rate) (Table 3).

### Table 1
Comparison of Characteristics in Different Groups

|            | Group A |   | Group B |   | F-ratio | P  |
|------------|---------|---|---------|---|---------|----|
|            | A1      | A2 | A3      | B1 | B2      | B3 |
| Age (in years) | 4.5± 4.70± 4.40± 4.30± 4.40± 4.50± 1.64 NS |   |         | 2.0 | 1.80 | 1.90 | 2.0 | 2.10 | 2.0 | 2.0 |
| Sex | 10 M 9 M 10 M 12 M 11 M 10 M |   | 10 F 11 F 10 F 8 F 9 F 10 F | χ² = NS |   | 1.86 |
| Weight (in Kg) | 17.4± 18.0± 18.60± 18.80± 18.70± 18.70± 2.4 NS |   | 4.9 | 5.0 | 4.80 | 5.20 | 5.60 | 5.20 |   |
| Height (in cm) | 80.0± 81.4± 81.6± 82.4± 81.4± 80.4± 2.82 NS |   | 5.20 | 6.20 | 7.80 | 8.40 | 7.40 | 6.82 |   |

NS = Not significant

### Table 2
Occurrence of Adverse events during attempted LMA placement

| Groups | No. | %  | No. | %  | No. | %  | No. | %  | No. | %  |
|--------|-----|----|-----|----|-----|----|-----|----|-----|----|
| A1     | 10  | 50 | 18  | 90 | 17  | 85 | 18  | 90 | 0   | 0  |
| A2     | 6   | 30 | 10  | 50 | 11  | 55 | 4   | 20 | 0   | 0  |
| A3     | 4   | 20 | 2   | 10 | 1   | 5  | 2   | 10 | 0   | 0  |
| B1     | 4   | 20 | 10  | 50 | 8   | 40 | 10  | 50 | 0   | 0  |
| B2     | 1   | 5  | 3   | 15 | 3   | 15 | 6   | 30 | 0   | 0  |
| B3     | 0   | 0  | 1   | 5  | 0   | 0  | 2   | 10 | 0   | 0  |
| Comparison χ² | P  |    | χ² | P  |    | χ² | P  |    | χ² | P  |
| A1 vs B1 | 3.96 | 0.05 | 7.61 | <0.001 | 8.64 | <0.01 | 7.61 | <0.01 | 0  | 1  |
| A2 vs B2 | 4.33 | 0.03 | 5.44 | <0.02 | 7.03 | <0.008 | 0.52 | 0.48 | 0  | 1  |
| A3 vs B3 | 4.33 | 0.03 | 0.35 | 0.55 | 1.00 | 0.32 | 0  | 1  | 0  | 1  |
During comparison of successful placement of LMA among subgroups, statistically significant difference was not found in A1 vs B1, but for A2 vs B2 and A3 vs B3, success rate was high in subgroup B3, which was statistically significant (p<0.05). (Table 3)

There was a significant fall in MAP and HR in all the subgroups of group A and B from its baseline after induction with propofol (before insertion), with maximum decrease in Group B3 (p<0.001).

After insertion of LMA, there was significant increase in MAP from baseline (BL) in A1 and A2 (p<0.01) while maximum in A3 (p<0.001). Similarly, there was increase in MAP and HR in all the subgroups of Group B but not stastically significant as compared to baseline (p>0.05). However, between group A and B, the increase was significant in all the subgroups of A as compared to their respective subgroups of After 5 minutes and 10 minutes we found a gradual decrease in MAP in all the subgroups of A and B. When compared these changes with the baseline (BL) statistically, it was significant (p<0.05) in group A but at 5 minutes the decrease was not significant from the baseline in subgroup B1, B2 and B3.

At 10 minutes the decrease in MAP in subgroup B1 was not significant from the baseline (60.0±2.90), while significant decrease in MAP in subgroup B2 and B3 i.e. 55±3.60 mm Hg and 57±2.1 mm Hg.

There was no significant difference in SpO2 before insertion, just after insertion, and at 5, 10 minutes post insertion from baseline in all the groups.

**DISCUSSION**

The present study which was done to determine the effect of midazolam premedication on dose of propofol in children premedicated with for insertion of LMA and to observe haemodynamic changes before induction, during and after insertion of LMA. Premedication with midazolam reduces the dose of propofol from 5mg kg\(^{-1}\) to 4mg kg\(^{-1}\) with even more successful insertion of LMA in 90% of children. The occurrence of adverse events during LMA placement like inadequate jaw relaxation, limb movements, gagging and coughing were higher in subgroups of A (propofol) as compared to their respective subgroups of B (midazolam + propofol). The incidence of adverse events decreased with increase in propofol dose and this trend was seen in both the groups. Brown et. al.\(^4\) have suggested propofol as a better induction agent due to decreased incidence of coughing and gagging with propofol than thiopentone as it has a greater depressant effect on airway reflexes than thiopentone.\(^4,5\)

Effective dose of propofol in midazolam premedicated group was significantly less than propofol alone group. ED50 and ED90 of unpremedicated children were 3.8mg kg\(^{-1}\) and 5.4mg kg\(^{-1}\) respectively and those of premedicated children were 2.6mg kg\(^{-1}\) and 3.6mg kg\(^{-1}\) respectively.\(^10\) The difference in effective doses between premedicated and unpremedicated children was highly significant (p<0.001). Coughing, gagging and laryngospasm may occur when depth of anesthesia is too light i.e. if lower doses of propofol are used\(^11\).

Increased induction requirements for propofol in children may be due to large central volume of distribution of drug\(^6,7\) and a greater cardiac output per kilogram body weight, which should result in lower peak concentration of propofol in blood, perfusing the brain after bolus injection. Synergistic actions of midazolam and propofol found in the present study are also supported by Short and Chiu\(^8\) where they suggested that the dose of propofol required to produce

**Table 3**

Successful Placement of LMA

| Group A | Group B |
|---------|---------|
| A1      | B1      |
| A2      | B2      |
| A3      | B3      |
| No.     | %       |
| 2       | 10%     |
| 6       | 30%     |
| 12      | 60%     |
| 5       | 25%     |
| 16      | 80%     |
| 20      | 100%    |

**Table 3a**

Successful placement of LMA among different subgroups

| Comparison | \(\chi^2\) | \(P\) |
|------------|-----------|-------|
| A1 vs B1   | 1.558     | 0.212 |
| A2 vs B2   | 10.101    | 0.001 |
| A3 vs B3   | 10.00     | 0.002 |

**Table 4**

Comparison of Mean arterial pressure (mm Hg) and heart Rate (HR/ min)

| Group | Baseline (BL) | Before insertion (BI) | After insertion (AI) | 5 min after insertion (5M) | 10 min after insertion (10M) |
|-------|---------------|-----------------------|----------------------|----------------------------|------------------------------|
| A1    | 120±5.6/ 60±5.0 | 115±4.9/ 55.0±4.20 | 135.0±5.1/ 65.0±4.30 | 122.0±5.20/ 57.0±3.2 | 120.0±5.40/ 56.6±3.40 |
| A2    | 122±4.2/ 62.0±3.4 | 117±5.6/ 58.0±3.6 | 137.2±4.4/ 66±4.10 | 124.0±4.6/ 58.4±3.8 | 124.0±4.8/ 58.2±3.9 |
| A3    | 118±4.10/ 61.0±3.2 | 113±4.3/ 56.0±3.4 | 133.0±4.2/ 65.0±3.1 | 120.0±5.20/ 57.1±3.2 | 120.0±4.0/ 57.2±3.4 |
| B1    | 120±5.2/ 60.0±4.20 | 112.0±4.6/ 56.00±3.20 | 123±6.80/ 60.0±3.40 | 122±4.80/ 59.0±3.20 | 120±4.80/ 57.2±3.4 |
| B2    | 120.2±5.30/ 59.0±3.20 | 112.0±5.20/ 55.0±3.40 | 123.20±6.60/61.0±3.60 | 122.60±4.60/ 59.0±3.60 | 115.20±4.80/55.0±3.60 |
| B3    | 120.4±4.60/ 61.0±3.40 | 105.8±5.40/ 50.0±2.90 | 123.60±6.80/63.0±3.40 | 122.2±4.82/ 61.0±2.50 | 114.2±3.40/ 57.0±2.10 |

Values mean + SD MAP/HR
anaesthesia was reduced by 52% in the presence of midazolam (p<0.01) and the coefficient of synergism being 0.78. ED50 of propofol was reduced from 1.93 mg kg\(^{-1}\) to 0.93 mg kg\(^{-1}\) with the addition of midazolam 0.13 mg kg\(^{-1}\). They postulated a role of CNS GABAA receptors in mediating sedation caused by propofol and midazolam. Midazolam was used as it does not enhance airway reactivity and has a shorter elimination half life (1-4 min).\(^9\)\(^{12}\)

Several investigators have commented on minimal haemodynamic changes. Interestingly, Martlew et al. 1996 did not observe any difference in cardiorespiratory side effects between low and high dose of propofol, unlike our present study. Short and Chui, 1991 observed in their study that there was a decrease in systolic, diastolic and mean arterial pressure when propofol was used alone or along with midazolam group (p<0.01), but there was no correlation between increasing dose and magnitude of change in arterial pressure\(^9\). When they compared the changes in arterial pressure produced by propofol with propofol-midazolam combination for anaesthesia, there was no difference between the two treatments. The current study also shows no significant change in MAP & HR after induction between two groups except in group B3 (5 mg kg\(^{-1}\) dose) where there was significant decrease in MAP and HR than in the propofol alone group. Our findings correlates with the observations of Goyagi et al. who found a significant decrease before insertion (after propofol induction with 1.95-2.6 mg kg\(^{-1}\)) in diastolic blood pressure (DBP), systolic blood pressure (SBP) and HR from preinduction values. After insertion, a significant increase was seen in SBP and HR (p<0.05), but increase in DBP was not statistically significant. At 5 minutes, all the values (SBP and DBP) decreased significantly from preinduction values may be due to deepening of anesthesia\(^{13}\). The inference that can be drawn from the present data is that addition of midazolam as a premedicant provides more haemodynamic stability than propofol alone during LMA placement. Both 5 mg kg\(^{-1}\) and 4 mg kg\(^{-1}\) propofol are found to be effective in propofol-midazolam group for LMA insertion. Since the fall in MAP is found to be significantly more after induction within the group and between the groups with 5 mg kg\(^{-1}\) of propofol, we can infer that 4 mg kg\(^{-1}\) is optimum dose of propofol with midazolam premedication for LMA insertion.

It may be concluded that midazolam premedication by reduces the dose of propofol and provides a better condition for placement of LMA in children without causing significant hemodynamic instability.

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