Comparison of propofol (1%) with admixture (1:1) of thiopentone (1.25%) and propofol (0.5%) for laryngeal mask airway insertion in children undergoing elective eye surgery: Double-masked randomized clinical trial

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ABSTRACT
Intravenous propofol 1% has been the preferred agent for Laryngeal Mask Airway (LMA) insertion. Admixture of thiopentone 1.25% and propofol 0.5% (1:1) has been used by various authors for induction as well as insertion of LMA in adults. There is no previous report where this admixture has been used for insertion of LMA in children. This study has been designed to investigate whether this admixture can be a suitable alternative to propofol, in relation to ease of insertion of the LMA, haemodynamic stability, cost containment, pain on injection and recovery in children. In this randomized, double-masked study, 50 ASA grade 1 and 2 patients of age 3 – 15 years and weighing more than 10 kg were included. The patients were divided into two groups; the P group received propofol 1%, while the Ad group received an admixture of thiopentone 1.25% and propofol 0.5% (1:1). All the children were evaluated for incidence of apnoea, pain on injection, jaw relaxation, ease of LMA insertion, coughing, gagging, laryngospasm, involuntary limb movements, incidence of hypotension and recovery. The demographic data, incidence of apnoea, pain on injection, jaw relaxation, ease of LMA insertion, coughing, gagging and involuntary movements were comparable in both groups. In the P group recovery was faster as compared to the Ad group. The admixture was cost effective as compared to Propofol alone [Indian National Rupees (INR) 24.64 ± 7.62 vs. INR 48.75 ± 23.25] (P = 0.001)). Admixture of propofol and thiopentone was a cheap, safe and effective alternative to propofol alone, for LMA insertion in children.

Key words: Admixture of propofol and thiopentone, LMA, paediatric

INTRODUCTION
The laryngeal mask airway (LMA) is commonly used for providing general anaesthesia in children, in anaesthetic practice, as it allows the maintenance of a clear airway while enabling the anaesthesiologist to keep both hands free and give full access of the operative field to the surgeon, especially in ophthalmic surgery.

Intravenous propofol (1%) has been the preferred induction agent for LMA insertion till date. It provides smooth induction with depression of airway reflexes, allowing easier insertion of LMA with a reduced incidence of side effects such as coughing, gagging or laryngospasm and rapid awakening.\(^1\) However, propofol is expensive and causes pain at the injection site, which can be reduced by admixture with lignocaine or less conveniently by prior administration of thiopentone.\(^2,3\)

Thiopentone 1.25% and propofol 0.5% admixture (1:1)
has been used by various authors for induction, as well as for insertion of LMA in adults, without many side effects. However, there are no previous reports of the use of this admixture to facilitate LMA insertion in children. We planned this study to investigate whether the admixture of thiopentone and propofol (1:1) can be a suitable alternative to propofol in relation to ease the insertion of LMA and for haemodynamic stability, cost containment, pain on injection and recovery in paediatric patients.

**METHODS**

Following approval of the institutional ethics committee, 50 children of ASA class I and II, belonging to either sex, of age 3 – 15 years, weighing more than 10 kg and scheduled for elective ophthalmic surgery, were included in the study. Children who were at risk of regurgitation, with known allergy to either agents, or with difficult airway were excluded. Children were prospectively, randomly allocated by the envelope method and the investigator and observer were blinded. In the preoperative room, with the child in the mother’s lap, a 22 gauge cannula was inserted on the dorsum of the non-dominant hand.

Intravenous induction agents were prepared in 10 ml syringes, for Propofol group (P), 10 ml of propofol 1% was mixed with 10 mg of lignocaine (preservative-free) and for Admixture group (Ad), thiopentone 2.5% was mixed with propofol 1% in a 1:1 ratio to make it thiopentone 1.25% and propofol 0.5% per ml. They were indistinguishable from each other and strict measures were taken to avoid cross contamination. The admixture syringes were stored at operating theatre room temperature (21 to 23°C) and were used within 24 hours.

The parents were allowed in the operation suite and after application of standard monitoring, including heart rate (HR), electrocardiography (ECG), oxygen saturation (SpO₂), and non-invasive blood pressure (NIBP); intravenous fentanyl 1.5 mcg/kg was administered 120 seconds prior to induction. The induction agent (0.25 ml/kg) was given over 30 seconds and the children were asked for pain or discomfort in the injection site till the children were conscious. An appropriate size LMA was inserted by an experienced anaesthesiologist (having > three years training in anaesthesia) blinded to drugs. Additional boluses of the induction agent were administered in 0.5 ml aliquots to deepen the anaesthesia, whenever required.

Adverse responses to airway manipulation, such as, coughing, gagging, laryngospasm and involuntary limb movement were graded as mild, moderate and severe [Table 1]. The ease of insertion of LMA and jaw relaxation were graded as excellent, satisfactory and poor [Table 2].

Incidence of apnoea (absence of spontaneous respiration for > 20 seconds) was noted in the children and they were ventilated with 100% O₂ before LMA insertion. After LMA insertion, anaesthesia was maintained with 33% oxygen in 67% nitrous oxide, and isoflurane, to maintain MAC 1.3. If the apnoea persisted or EtCO₂ > 45 mmHg, ventilation was assisted manually. The occurrence of hypotension was noted and treated with ringer lactate at a rate of 4 ml/kg/hr. At the end of surgery, after LMA removal, recovery was evaluated by using the Aldrete score [0 – 10 range] [Table 3]. If there were any incidences of postoperative nausea and vomiting and complications, they were noted. The acquisition cost of the drug was calculated using the mean dose required for LMA insertion in both groups.

The demographic data, dose of drug and Aldrete score were analysed using the analysis of variance (ANOVA) test. The incidence of adverse response to airway manipulation, such as, coughing, gagging, laryngospasm, involuntary limb movements, jaw relaxation and ease of LMA insertion was analysed using the Chi square test with Fisher exact test, wherever appropriate.

| Parameters: Coughing, gagging, laryngospasm and involuntary limb movements |
|---|---|
| 1 Mild | Transient and minimal lasting < 5 seconds |
| 2 Moderate | Lasted > 5 seconds, but resolved spontaneously within 20 seconds |
| 3 Severe | Sustained > 20 seconds or required additional boluses of drugs |

| 1 Excellent | No adverse responses |
| 2 Satisfactory | Adverse response to airway manipulations, but not affecting the insertion of LMA |
| 3 Poor | a. Moderate-to-severe adverse responses requiring additional boluses of drugs b. More than two attempts were required for LMA insertion |

LMA: Laryngeal mask airway
RESULTS

The demographic data were comparable in both the groups [Table 4]. Mean volume required for induction in the Ad group was $5.5 \pm 1.7$ ml and in the P group was $6.5 \pm 3.1$ ml [Table 5], that is, $27.5 \pm 8.5$ mg of propofol in the Ad group and $65 \pm 31$ mg of propofol in the P group. Pain on injection was absent in both groups. The requirement of additional boluses of induction agent was also comparable and the mean rescue dose was comparable statistically. The incidence of adverse responses to airway manipulation, such as, coughing, gagging, laryngospasm, involuntary limb movements, incidence of apnoea and hypotension were comparable [Tables 5 and 6].

In the Ad group, excellent jaw relaxation and LMA insertion was seen in 17 (68%) patients and the same was observed in 13 (52%) patients in the P group [Figure 1]. Recovery was faster in the P group as compared to the Ad group ($P < 0.001$) [Table 5].

The total cost in the Ad group was Indian National Rupees (INR) $24.64 \pm 7.62$ and in the P group it was INR $48.75 \pm 23.25$ ($P = 0.001$) [Table 5].

DISCUSSION

The laryngeal mask airway provides a direct connection to the tracheal airway without the need for laryngoscopy and tracheal intubation\(^6\) and there is a decrease in the incidence of arterial oxygen desaturation, less airway stimulation and liberation of the anaesthesiologist to attend to other responsibilities. Changes in intraocular pressure are also blunted with the use of LMA as compared to endotracheal intubation.\(^7\)

Successful insertion of LMA requires an adequate depth of anaesthesia by the use of either inhalation or intravenous agents to suppress pharyngeal and laryngeal reflexes.

To date, for LMA insertion, propofol is the agent of choice for intravenous induction, as it provides rapid induction with excellent jaw relaxation, but it has disadvantages such as pain at the injection site, involuntary limb movements, prolonged apnoea and hypotension.

| Table 3: Aldrete’s post-anaesthesia recovery scoring system\(^5\) (Range: 0 – 10) |
| --- |
| **Score** |
| **Activity** |
| Able to move all four limbs | 2 |
| Able to move only two limbs | 1 |
| Not able to move any limb | 0 |
| **Respiration** |
| Able to breathe deeply and cough freely | 2 |
| Limited respiratory effort or dyspnoea | 1 |
| No spontaneous respiratory activity | 0 |
| **Circulation** |
| SBP was $\pm 20\%$ of the per anaesthetic level | 2 |
| SBP was between 20 and 50$\%$ of the pre-anaesthetic level | 1 |
| SBP alteration was $\pm 50\%$ or more | 0 |
| **Consciousness** |
| Fully alert, evidence by the ability to answer questions | 2 |
| Aroused only by calling their names | 1 |
| Auditing stimulation failed to elicit a response | 0 |
| **Colour** |
| Obvious normal or pink colour | 2 |
| Pale, dusty or blotchy discoloration as well as jaundice | 1 |
| Frank cyanotic | 0 |

| Table 4: Demographic characteristics and duration of surgery (mean ± SD) |
| --- |
| **Ad group (n = 25)** | **P group (n = 25)** |
| **Age (years)** | 8.24 ± 2.8 | 10.0 ± 3.8 |
| **Weight (kg)** | 21.92 ± 7.0 | 26.0 ± 12.3 |
| **Sex (M/F)** | 19/6 | 15/10 |
| **Duration of surgery (min)** | 34.56 ± 14.9 | 59.2 ± 28.9* |

Ad – Admixture of thiopentone (1.25%) and propofol (0.5%) (1:1), P – Propofol (1%), *$P < 0.001$ |

| Table 5: Dose, side effects of induction agent and recovery (mean ± SD) (%) |
| --- |
| **Assessment** | **Ad group (n = 25)** | **P group (n = 25)** |
| **Dose (ml)** | $5.5 \pm 1.7$ | $6.5 \pm 3.1$ |
| No. of patients requiring additional boluses of induction agents | 4 (16) | 3 (12) |
| Incidence of apnoea | 6 (24) | 11 (44) |
| Incidence of hypotension | 7 (28) | 11 (44) |
| Time to reach aldrete 10 (min) | $35.8 \pm 12.2$ | $10.72 \pm 10.5^*$ |
| PONV | 0 | 0 |
| Mean cost of induction agent per child (INR) | $24.64 \pm 7.62$ | $48.75 \pm 23.25^*$ |

Ad – Admixture of thiopentone (1.25%) and propofol (0.5%) (1:1), P – Propofol (1%), INR - Indian National Rupees, *$P \leq 0.001$, figures in parentheses are in percentages

| Table 6: Incidence of adverse response to airway manipulation |
| --- |
| **Adverse effects** | **Ad group (n = 25)** | **P group (n = 25)** |
| Inadequate jaw relaxation | 4 (16) | 4 (16) |
| Coughing | 0 | 3 (12) |
| Gagging | 3 (12) | 1 (4) |
| Laryngospasm | 1 (4) | 0 |
| Involuntary limb movement | 10 (40) | 14 (56) |

Ad – Admixture of thiopentone (1.25%) and propofol (0.5%) (1:1), P – Propofol (1%), NS – not significant, figures in parentheses are in percentages
Thiopentone has the advantage of painless injection and less incidence of hypotension, although it does not provide good jaw relaxation and can cause coughing, gagging and laryngospasm when used alone for LMA insertion.\[8\] It has been used with prior topical lignocaine spray to the posterior pharyngeal wall or co-induction with intravenous midazolam for LMA insertion in adults.\[9\]

Admixture of thiopentone and propofol is compatible and stable\[10-12\] due to its bactericidal properties, as it does not support the growth of micro-organisms despite the presence of nutrients in the admixture.\[13\] This admixture has a synergistic interaction\[14\] and does not prolong recovery when used for induction of anaesthesia and may reduce the incidence of convulsion. Cherin and Smiler took this admixture as an example of cost containment, while taking advantage of both the drugs, as it can be used for 24 hours if kept at operating room temperature (21 – 23ºC), further decreasing wastage of drugs and thereby being more cost effective.\[16\] This admixture was used successfully for the induction of anaesthesia in adults.

Pain on injection can be considered a minor complication, but it may cause distress to the child and reduces acceptability of an otherwise useful agent. The cause of pain with propofol injection is due to the activation of kininogens\[17\] or to the free aqueous concentration of propofol in the emulsion.\[18\] Thiopentone reduces pain caused by propofol due to decrease in the release of kinins and change in the pH of the admixture. Jones D et al. showed that adding thiopentone to propofol could be as efficacious in preventing injection pain as mixing lignocaine 40 mg with 20-ml propofol. However, Lee TW et al. found thiopentone pre-treatment to be more effective than lignocaine.\[2\] In our study, none of the children in both the groups complained of pain on injection, which was similar to the study by Kau YC et al.\[19\] However, these studies were done in adults where pain evaluation is easier.

A study conducted by T. Goyagi et al. concluded that pre-treatment with fentanyl 2 mcg/kg\(^{-1}\) reduced the propofol requirement by 60% for LMA insertion,\[20\] hence, we used fentanyl 1.5 mcg/kg\(^{-1}\) before induction in both the groups and observed that the dose of propofol in paediatric patients was comparable to the adult dose used in the previous studies. A mean dose of propofol in the Ad group was half of that compared to the P group, suggesting an additive action of both the drugs, which was in confirmation with the studies of Yeo KSJ et al.\[1\] and Jones et al.\[4\] and explained by similar binding sites on the gamma-aminobutyric acid-A (GABA-A) receptors for propofol and barbiturates.\[21\] However, Naguib and Sari-Kouzel\[14\] demonstrated that sequential intravenous administration of thiopentone and propofol caused a synergistic interaction between them.

In our study, the condition for LMA insertion was excellent in 68% of the patients in the Ad group as compared to 52% in the P group, but this difference was statistically not significant while the incidence of various adverse responses to airway manipulation were similar in both the groups. Yeo KSJ et al.\[1\] found excellent conditions for LMA insertion in 65% of the patients in the P group as compared with 48.8% in the Ad group. This is in contrast to our finding and may be attributed to the paediatric population in our study.

There was a significant difference in the duration of surgery between the groups in our study, but this did not affect our results, as our main area of study was during induction and LMA insertion.

A fall in systolic blood pressure during propofol induction has been consistently reported in literature.\[22\] A decrease in the dose of propofol in the Ad group causes a decreased effect on afterload and the myocardium.\[23\] A decrease in the rate of administration of propofol decreases not only the dose required for induction, but also the degree of haemodynamic change.\[24\] In our study, the incidence of side effects such as the incidence of apnoea and hypotension were similar. Recovery in the P group was better as compared to the
admixture group in our study, but this had no effect of the Post Anaesthesia Care Unit (PACU) discharge. Similar results were observed by Kern C et al.[25] in the adult population.

In our study, the admixture of thiopentone and propofol reduced the cost by half, as compared to propofol alone (INR 24.64 ± 7.62 vs. INR 48.75 ± 23.25), which can be of significance for paediatric population in developing countries, who come for repeated surgeries including examination under anaesthesia.

In conclusion, the admixture of thiopentone (1.25%) and propofol (0.5%) (1:1) is an acceptable and satisfactory alternative to propofol (1%) for induction of anaesthesia and LMA insertion in paediatric population.

REFERENCES

1. Yeo KS, Kua SW, Teoh GS, Ongsiong MK. The use of thiopentone/propofol admixture for laryngeal mask airway insertion. Anaesth Intensive Care 2001;29:38-42.
2. Lee TW, Loewenthal AE, Strachan JA, Todd BD. Pain during injection of propofol, the effect of prior administration of thiopentone. Anaesthesia 1994;49:817-8.
3. Haugen RD, Vaghadia H, Waters T, Merrick PM. Thiopentone pretreatment for propofol injection pain in ambulatory patients. Can J Anaesth 1995;42:1108-12.
4. Jones D, Prankerd R, Lang C, Chillers M, Bignell S, Short T. Propofol – thiopentone admixture – Hypnotic dose, pain on injection and effect on blood pressure. Anaesth Intensive Care 1999;27:346-56.
5. Aldrete JA, Kroulik D. A postoperative recovery score. Anesth Analg 1970;49:924-34.
6. Brain AI, McGhee TD, McAteer EJ, Thomas A, Abu-Saad MA, Bushman JA. The laryngeal mask airway. Development and preliminary trials of a new type of airway. Anaesthesia 1985;40:356-61.
7. Watcha MF, White PF, Tychsen L, Stevens JL. Comparative effects of laryngeal mask airway and endotracheal tube insertion on intraocular pressure in children. Anesth Analg 1992;75:355-60.
8. Scanlon P, Carey M, Power M, Kirby F. Patient response to laryngeal mask insertion after induction of anaesthesia with propofol or thiopentone. Can J Anaesth 1993;40:816-8.
9. Bapat P, Joshi RN, Young E, Jago RH. Comparison of propofol versus thiopentone with midazolam or lignocaine to facilitate laryngeal mask insertion. Can J Anaesth 1996;43:546-8.
10. Chermin EL, Stewart JT, Smiler B. Stability of thiopentone sodium and propofol on polypropylene syringes at 23 and 24°C. Am J Health Syst Pharm 1996;53:1576-9.
11. Prankerd RJ, Jones RD. Physiochemical compatibility of propofol with thiopentone sodium. Am J Health Syst Pharm 1996;53:2606-10.
12. Lazar ER, Jolly DT, Tam YK, Hrazdil J, Tawfik SR, Clanachan AS. Propofol and thiopentone in a 1:1 volume mixture is chemically stable. Anesth Analg 1998;86:422-6.
13. Crowther J, Hrazdil J, Jolly DT, Galbraith JC, Greacen M, Grace M. Growth of micro organism in propofol, thiopental and a 1:1 mixture of propofol and thiopental. Anesth Analg 1996;82:475-8.
14. Naguib M, Sari-Kouzel A. Thiopentone – propofol hypnotic synergism in patients. Br J Anaesth 1991;67:4-6.
15. Paw HG, Garrood M, Fylly-Gravis AJ, Rich GT. Thiopentone and propofol: a compatible mixture? Eur J Anaesthesiol 1998;15:409-13.
16. Cherin EL, Smiler B. Propofol – thiopentone admixture: Implication for cost savings and clinical use. Am J Anaesthesiol 1997;24:251-3.
17. Scott RP, Saunders DA, Norman J. Propofol: Clinical strategies for preventing the pain of injection. Anaesthesia 1988;43:492-4.
18. Klement W, Arndt JO. Pain on injection of propofol: effects of concentration and diluent. Br J Anaesth 1991;67:281-4.
19. Kau YC, Wu RS, Cheng KS. Propofol-sodium thiopental admixture reduces pain on injection. Acta Anaesthesiol Sin 2000;38:9-13.
20. Goyagi T, Tanaka M, Nishikawa T. Fentanyl decreases propofol requirement for laryngeal mask airway insertion. Acta Anaesthesiol Scand 2003;47:771-4.
21. Whittington MA, Jefferys JG, Traub RD. Effects of intravenous anesthetic agents on fast inhibitory oscillations in the rat hippocampus in vitro. Br J Pharm 1996;118:1977-86.
22. Gauss A, Heinrich H, Wilder-Smith OH. Echocardiographic assessment of the haemodynamic effects of propofol: a comparison with etomidate and thiopentone. Anaesthesia 1991;46:99-105.
23. Brüssel T, Theissen JL, Vigfusson G, Lankenheimer PP, Van Aken H, Lawin P. Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. Anesth Analg 1989;69:35-40.
24. Stokes DN, Hutton P. Rate-dependent induction phenomena with propofol: implication for the relative potency of intravenous anesthetics. Anesth Analg 1991;72:578-83.
25. Kern C, Weber A, Aurilio C, Forster A. Patient evaluation and comparison of the recovery profile between propofol and thiopentone as induction agents in day surgery. Anaesth Intensive Care 1998;26:156-61.

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