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Comparison between effects of ketamine and midazolam as co-induction agents with propofol for proseal™ laryngeal mask insertion

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Introduction: Optimal conditions during supraglottic airway placement are important to prevent adverse events associated with inadequate depth of anaesthesia. This study compared propofol co-induction with ketamine or midazolam during ProSeal™ Laryngeal Mask Airway (PLMA) insertion.

Materials and Methods: A total of 118 ASA I or II patients aged between 18 to 60 years requiring PLMA insertion for surgery were recruited into this prospective, randomised and double blind study. Patients were grouped into propofol (2mg/kg) co-induction with either ketamine (0.5mg/kg) or midazolam (0.03mg/kg). During PLMA insertion, the degree of mouth opening, ease of insertion, swallowing, coughing or gagging, movement and laryngospasm were scored and haemodynamic changes were recorded. Overall insertion conditions were further graded into excellent, good, poor or unacceptable.

Results: The ketamine-propofol group had significantly better mouth opening (p=0.01) and shorter duration of apnoea (p<0.001). Other conditions during PLMA insertion and the overall grading were comparable between groups. Haemodynamic parameters were comparable to baseline within each group. However, the ketamine-propofol group had more stable blood pressure readings and maintained a higher heart rate (p<0.05) compared to the midazolam-propofol group.

Conclusion: Propofol co-induction with either ketamine or midazolam conferred comparable PLMA placement conditions.

Keywords: propofol; co-induction; ketamine; midazolam, proseal™ laryngeal mask insertion

Introduction

Managing the airway remains a core and important anaesthetists' skill.[1] Brain et al first introduced the non-invasive supraglottic airway device (SAD) called the laryngeal mask airway™ (LMA) to begin a new era in airway management.[2] It has since become an invaluable template for newer generations of airway devices. A second generation SAD, the ProSeal™ laryngeal mask airway (PLMA) is an improved version which allows higher sealing pressures and oesophageal drainage to prevent gastric aspiration and insufflation.[3]

Successful insertion of the LMA requires optimum anaesthetic depth to avoid unwanted airway reflexes such as swallowing, gagging, coughing or involuntary movements to severe complications such as laryngospasm.[1-2]

Satisfactory anaesthetic induction conditions are best provided by propofol compared to other intravenous induction agents.[4] However, when propofol was used as a single induction agent in unpremedicated patients, doses exceeding 2.5 mg/kg were required to allow smooth and atraumatic LMA insertion.[5] Elevated propofol doses are not desirable as the cardiorespiratory depression is dose dependant.[6]

Ketamine, an N-methyl d-aspartate (NMDA) receptor antagonist, has beneficial airway-maintaining and sympathomimetic effects when used as a co-induction agent at sub-anaesthetic

doses.[4,7] Midazolam, a short acting benzodiazepine has been shown to attenuate propofol related cardio-respiratory depressant effects and at the same time reduces the risk for awareness with its anterograde amnesic effects.[8] Our study compared the effects of these two drugs as co-induction agents with propofol for PLMA insertion in adults as the literature has thus far, only compared them in children.[9]

Materials and Methods

This prospective, randomised, double blind comparative study was conducted following institutional approval. A total of 118 patients with American Society of Anaesthesiologists (ASA) physical status Class I or II, aged between 18 to 60 years old scheduled for elective surgeries requiring PLMA insertion were enrolled. Patients with hyper-reactive airway disease, anticipated difficult airway, body mass index (BMI) > 35 kg/m^2, gastric aspiration risk, allergy to study drugs and those on regular sedatives, psychiatric medications or β-blockers were excluded.

Explanation about the study and written informed consent was obtained from recruited patients during preoperative assessment. All patients were fasted for 6 hours and no sedative premedication was given. Demographic data including age, weight, height, gender and ASA status were recorded. They were randomly allocated into 2 groups, Group K (Ketamine) and Group M (Midazolam) using computer generated random numbers. One anaesthetic doctor prepared and administered the drugs while another who was blinded to the study drugs, inserted the PLMA and assessed the insertion conditions. Insertion of the PLMA was done by an anaesthetic registrar in-charge of that operating room, having at least 3 years anaesthetic experience and familiar with the introducer technique of PLMA insertion. The study protocol was given and explained to both the anaesthetic doctors involved prior to patient induction.

In the operating theatre, standard monitoring was applied including electrocardiogram (ECG), non-invasive blood pressure (NIBP) and pulse oximetry prior to induction of anaesthesia. The PLMA size, maximum cuff inflation volume and oro-gastric tube size were selected based on the patient's weight.[10] All patients were hydrated with 5ml/kg Hartmann's solution via a 20G intravenous cannula.

Patients were pre-oxygenated with 100% oxygen at 6 L/minute for 3 minutes. The study drug was injected over 10 seconds following preoxygenation. Group K received i.v. ketamine 0.5mg/kg while Group M received i.v. midazolam 0.03mg/kg, each diluted to 10ml with normal saline. After 2 minutes, i.v. propofol 2mg/kg was administered over 15 seconds.

Insertion of PLMA using the introducer technique was performed 60 seconds after propofol administration when the patient's jaw relaxed. The overall insertion condition was graded according to the modified scheme of Lund and Stovener into either excellent (no gagging or coughing, no patient movement or laryngospasm), good (mild to moderate gagging, coughing or patient movement with no laryngospasm), poor (moderate to severe gagging, coughing or patient movement with no laryngospasm) or unacceptable (severe gagging, coughing or patient movement or laryngospasm).[11] Further scoring of individual insertion conditions were assessed via a modified three point scale consisting of six variables.[12] These included resistance to mouth opening (1: full; 2: partial; 3: none), ease of insertion (1: easy; 2: difficult; 3: impossible), swallowing (1: nil; 2: slight; 3: gross), coughing or gagging (1: nil; 2: slight; 3: gross), head or limbs movement (1: nil; 2: slight; 3: gross) and laryngospasm (1: nil; 2: partial; 3: total). Following insertion, position of PLMA and airway patency was verified by sufficient tidal ventilation (6-10ml/kg), oxygen saturation (SpO_2) > 95% and capnograph ($ETCO_2$) readings (35-45mmHg).

A maximum of three PLMA insertion attempts were allowed per patient. In between PLMA insertion attempts, the patient's lungs were ventilated for 30 seconds using facemask with 100% oxygen devoid of volatile agents. Anaesthesia was maintained with boluses of i.v. propofol 0.5mg/kg titrated to patients' requirements. If PLMA insertion was unsuccessful, an alternative device such as endotracheal tube was to be used. However, the conditions during PLMA insertion were graded at the first attempt only. The total number of

attempts and any additional propofol doses given was recorded.

Patients were allowed to breathe spontaneously after successful PLMA insertion. Assisted manual ventilation was provided when the apnoeic period exceeded 30 seconds from time of PLMA insertion to ensure that the SpO_2 remained > 95%. Manual ventilation was ceased when adequate spontaneous respiration returned. The duration of apnoea was recorded via a digital timer as the time from the end of propofol injection until the return of adequate spontaneous ventilation. Thereafter, anaesthesia was maintained with sevoflurane 2-3% in oxygen(50%):air(50%) mixture until the minimum alveolar concentration (MAC) of 1.0 to 1.3 was achieved.

Non-invasive systolic, diastolic and mean arterial blood pressure (SBP, DBP and MAP respectively), heart rate (HR) and SpO_2 were recorded before induction of anaesthesia (baseline 0 min), and at intervals designated as 1 (study drug bolus administered), 2 (propofol bolus given), 3 (immediately after successful PLMA insertion) and at every one minute thereafter up to 3 minutes following PLMA insertion. Respiratory rate (RR) and $ETCO_2$ were recorded every minute for 5 minutes following a successful PLMA insertion.

Rescue i.v. ephedrine 6mg boluses were given when >20% reduction of MAP occurred and this was documented. Adverse incidences such as excessive secretions, lacrimation, breath-holding, post-operative emergence delirium or sedation were recorded.

Sample size was calculated using the PS Power and Sample Size Calculations program (version 3.0). Based on Goel et al (2008), 51 patients per arm were required to detect more than 20% change in SBP.[9] The power of the study was taken at 80% with a Type I error of 0.05. A total of 118 patients were recruited to include a drop-out rate estimated at 15%.

All data were analysed by SPSS statistical package programme (Version 22; IBM SPSS Inc Chicago, IL). Differences of numerical data between groups were evaluated using student's t-test. Categorical data were analysed with the Chi-Square test. A p value of <0.05 was regarded as statistically significant.

Results

A total of 118 patients were enrolled and none were excluded from the study as there was no incidence of failed PLMA insertion. There were no statistically significant differences in age, gender, BMI, ASA or types of surgeries between groups. Duration of surgery and anaesthesia were significantly longer in Group K.

Table 1: Demographic and operative data.

	Group K (n=59)	**Group M (n=59)**	***p* value**
Age (years)	42.5 ± 11.7	42.7 ± 12.3	0.928
Gender Male Female	 30 (50.8) 29 (49.2)	 29 (49.2) 30 (50.8)	1.000
BMI (kg/m^2)	25.4 ± 3.6	24.9 ± 3.5	0.446
ASA I II	 37 (62.7) 22 (37.3)	 31(52.5) 28 47.5)	0.352
Types of Surgery			
General Surgery	17 (28.8)	20(33.9)	0.250
Orthopaedic Surgery	26 (44.1)	15(25.4)	
Gynaecology	10 (16.9)	16(27.1)	
Others	6 (10.2)	8 (13.6)	
Duration of surgery (minutes)	51.2 ± 17.7	42.1 ± 15.9	0.004*
Duration of anaesthesia (minutes)	61.6 ± 17.8	54.1 ± 15.9	0.018*

* $p < 0.05$ considered as statistically significant.

Additional propofol doses were required more frequently in Group M although the total dose of propofol used was comparable between the two groups. Group M had a significantly longer apnoea time compared to Group K. The PLMA insertions were successfully performed at the first and second attempts in both groups. Only one patient in Group K required a third insertion attempt.

Table 2: Propofol induction doses, duration of apnoea and PLMA insertion.

	Group K (n=59)	Group M (n=59)	*p* value
Total propofol dose (mg)	130.7 ± 23.4	132.1 ± 25.1	0.755
Additional propofol required (no. of pts)	2 (3.4)	9 (15.3)	0.053
Duration of apnoea (minutes)	1.0 ± 0.6	1.8 ± 0.7	< 0.001*
Size of PLMA			
3	28 (47.5)	37 (62.7)	0.248
4	25 (42.4)	18 (30.5)	
5	6 (10.2)	4 (6.8)	
PLMA insertion attempts			
1	54 (91.5)	55 (93.2)	0.604
2	4 (6.8)	4 (6.8)	
3	1 (1.7)	0 (0)	

* $p < 0.05$ considered as statistically significant.

Group K had a significantly higher incidence of full mouth opening when compared to Group M (93.2% versus 76.3%). Head or limb movement were present in 35.6% and 27.1% of patients in Group K and Group M respectively. The sum of insertion scores ranged between a minimum of 6 and maximum of 9 in both groups.

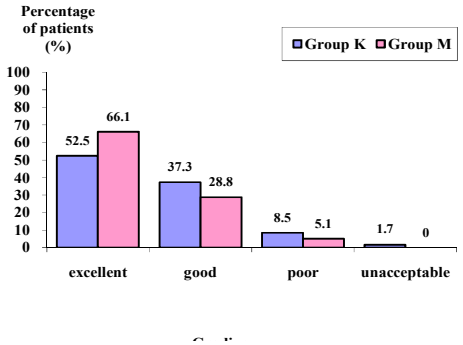
Table 3: Conditions during insertion of PLMA.

	Group K (n=59)	Group M (n=59)	*p* value
Mouth opening Full / Partial/None	55/4/0	45/14/0	0.019*
Ease of PLMA insertion Easy/Difficult/Impossible	53/6/0	55/4/0	0.743
Swallowing Nil / Slight/Gross	57/2/0	58/1/0	1.000
Coughing or gagging Nil / Slight/Gross	47/12/0	52/7/0	0.316
Head or limbs movement Nil / Slight/Gross	38/21/0	43/16/0	0.428
Laryngospasm Nil / Partial/Complete	58/1/0	59/0/0	1.000
Insertion condition summed score 6/7/8/9	27/20/10/2	32/14/11/ 2	0.675

* $p < 0.05$ considered as statistically significant.

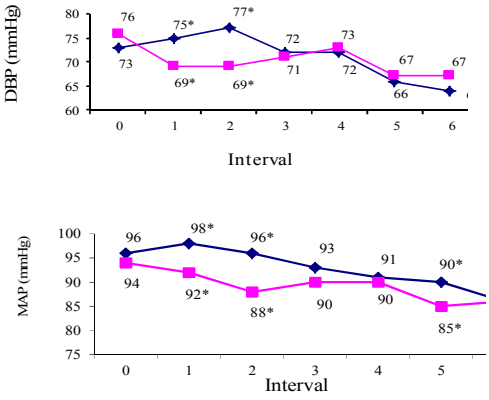
The overall insertion condition scores were comparable between groups. Group K and Group M had 89.8% and 94.9% satisfactory ('excellent' and 'good') conditions respectively. One patient in Group K had unacceptable grading.

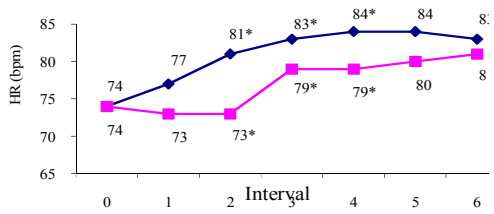
Figure 1: Overall grading of PLMA insertion conditions.



There were no statistically significant differences in the baseline SBP (p=0.901), DBP (p=0.260), MAP (p=0.340) and HR (p=0.928) readings between groups. When compared to Group M, Group K had significantly higher SBP at intervals 1 (p=0.001), 2 (p<0.001), 3 (p=0.006), 4 (p=0.030) and 5 (p<0.001). Group K also had significantly higher DBP at intervals 1 and 2 (p<0.001), higher MAP at intervals 1 (p<0.001), 2 (p<0.001) and 5 (p=0.001) with elevated HR at intervals 2 (p<0.001), 3 (p=0.030) and 4 (p=0.01).

Figure 2: Comparison of SBP, DBP, MAP and HR at various time intervals.





0 = baseline value; 1 = study drug bolus administered; 2 = propofol bolus given; 3 = immediately after successful PLMA insertion; 4; 5; 6 = 1, 2, 3 minutes after successful PLMA insertion.
(* Significant at $p < 0.05$)

Group K and Group M had 5 (8.5%) and 6 (10.2%) patients respectively experiencing post-operative sedative effects in the recovery area. None of the patients required any treatment. No other adverse incidences such as excessive secretions, lacrimation, breath-holding or postoperative emergence delirium were noted in both groups.

Discussion

'Co-induction' describes the practice of combining small doses of anaesthetic agents to reduce the overall dose of induction drugs required.[13] It allows a balance between therapeutic effects and the unwanted side effects.[14] Studies in children showed that 3.5 mg/kg propofol as the sole induction agent was required for good LMA insertion conditions.[4,15] Co-induction with either ketamine or midazolam further improved the LMA insertion conditions.[4, 15] In our study of adult patients, the total propofol dose used in both groups corresponded to an initial induction dose of 2 mg/kg with insignificant additional propofol doses thereafter. The satisfactory PLMA insertion conditions induced by an acceptably lower propofol dose due to co-induction agents reaffirm previous literature findings.[15]

Ketamine's additive effects are due to its antagonism on NMDA receptors.[9] In our study, both ketamine and midazolam provided comparable overall PLMA insertion conditions when co-induced with propofol. Co-induction with ketamine however, produced better full mouth opening, and hence, effective jaw relaxation. This was similarly reported by Yousef and Elsayed in their study on children.[16]

We found that co-induction with midazolam produced a significantly longer duration of apnoea compared to ketamine. This suppression of breathing effort is attributed to the synergistic action between midazolam and propofol at the common GABA receptor sites. Although this may have contributed to the high satisfactory scores during PLMA insertion, in practice this marginal time delay of 0.8 minutes was neither a major clinical advantage nor inconvenience. Opioids are known to improve the insertion conditions but with an associated prolonged apnoea duration.[3,6]

Airway manipulation stimulates the autonomic nervous system. Haemodynamic parameters can increase 20% after LMA insertion, with an additional 30% after orotracheal intubation.[1] We did not find any significant blood pressure and HR changes compared to baseline values in both the ketamine or midazolam co-induction groups. However, maintenance of haemodynamic parameters was better with the ketamine group who had significantly higher SBP, DBP, MAP and HR. This was most pronounced at the initiation of propofol bolus injection. The sympathomimetic action of ketamine offsets the sympatholytic effect of propofol leading to less notable haemodynamic reduction thereafter.[9] Utilising ketamine as a co-induction agent with propofol may be beneficial in unfit or elderly patients who are more susceptible to haemodynamic instability during induction of anaesthesia.

We found minimal and comparable undesired responses between ketamine and midazolam co-induction during PLMA placement. Movement of the head or limbs were the most frequently encountered. Propofol by itself is known to cause involuntary movements.[4] Patients who received the ketamine-propofol combination had marginally higher incidence of coughing or gagging, probably due to ketamine's ability to maintain airway reflexes.[9] Benzodiazepines on the other hand, are known to reduce upper airway reflexes.[9]

The main limitation in this study is the fact that a control group of propofol induction used alone was not included. The exclusion was intentional as unwanted haemodynamic instability was anticipated when higher propofol doses are solely used.

In conclusion, both propofol with either ketamine or midazolam as a co-induction agent provided overall comparable PLMA insertion conditions and preservation of baseline haemodynamic parameters. The ketamine-propofol combination had a shorter duration of apnoea, better mouth opening and haemodynamic profile when compared to the midazolam-propofol combination.

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