

A CLINICAL COMPARATIVE STUDY OF EFFECTIVENESS OF MIDAZOLAM 0.05mg.kg⁻¹ AS CO-INDUCTION AGENT WITH PROPOFOL 2.5mg.kg⁻¹ AND PROPOFOL 3.5mg.kg⁻¹ ALONE FOR LARYNGEAL MASK AIRWAY INSERTION IN CHILDRENAshwini S¹, Kempachary²**HOW TO CITE THIS ARTICLE:**

Ashwini S, Kempachary. "A Clinical Comparative Study of Effectiveness of Midazolam 0.05mg.kg⁻¹ as Co-Induction Agent with Propofol 2.5mg.kg⁻¹ and Propofol 3.5mg.kg⁻¹ Alone for Laryngeal Mask Airway Insertion in Children". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 25, March 26; Page: 4235-4243, DOI: 10.14260/jemds/2015/612

ABSTRACT: BACKGROUND AND OBJECTIVE: Propofol is a commonly used induction agent for insertion of laryngeal mask in children. When used as a sole agent, children require a larger dose of propofol than adults^{1,2,3} which may be associated with haemodynamic and respiratory effects like hypotension,^{3,4} bradycardia, apnoea, hypoventilation.⁴ These can be mitigated by 'co-induction' which is the practice of administering a small dose of a sedative or other anaesthetic agent to reduce the dose of induction agent.^{4,5,6,7,8,9} The present clinical study was undertaken to study the effectiveness of midazolam as co-induction agent with propofol in comparison to propofol alone for laryngeal mask insertion in children. **METHODS:** The study was conducted at Cheluvamba Hospital attached to MMC&RI, Mysore. Sixty children aged 3-10 years, ASA I, II undergoing elective short surgical procedures were randomly allocated into two groups of 30 each. All received syrup promethazine 0.3mg. kg⁻¹ the previous night and had EMLA cream applied on dorsum of both hands 1h before surgery. Patients in Group I received propofol 3.5 mg. kg⁻¹ and Group II received i. v. midazolam 0.05 mg. kg⁻¹ two minutes prior to propofol 2.5 mg. kg⁻¹. Propofol was mixed with lignocaine 0.5 mg. kg⁻¹ and given i. v. over a period of 30s and then LMA insertion characteristics (1) "Mouth opening" graded on a three-point scale i. e. full, partial and impossible and (2) "The ease of LMA insertion" graded on a four-point scale i. e. easy, some difficulty, difficult and impossible were assessed in the next 30s. The appropriate size LMA insertion was done. If insertion failed on first attempt, a bolus of 0.5 mg. kg⁻¹ propofol was given; if impossible, LMA use abandoned and alternative technique resorted. Anaesthesia maintained using 66% nitrous oxide, 33% oxygen and halothane, ventilation assisted, no surgical stimulus applied during 5 minute study period. The haemodynamic parameters were recorded immediately after midazolam, propofol (0 min) and thereafter at 1 minute interval for 5 minutes. Recovery was assessed and LMA removed once the child was awake, spontaneously breathing with adequate tidal volume. The observations were statistically evaluated using Frequencies and Crosstabs, Independent Samples t-test, Paired Sample t-test and Repeated measure ANOVA. **RESULTS:** The age, sex and weight distribution of patients were comparable among two groups. The mouth opening was full in 90% and 93.3% of patients while partial in 10% and 6.7% of patients in Groups I and II respectively. The LMA insertion was easy in 90% and 100% of patients in Groups I and II respectively while some difficulty and difficult insertion was observed in 6.7% and 3.3% of Group I patients. Neither mouth opening nor LMA insertion was impossible in both the groups. Coughing, gagging, laryngospasm and desaturation were not observed in both the groups. The heart rate and blood pressure showed reduction (p<0.05) compared to its basal value in Group I while it showed gradual and less reduction (p <0.05) in Group II, but not amounting to bradycardia,

ORIGINAL ARTICLE

hypotension. The duration of anaesthesia was comparable among the groups without undue delay in recovery in Group II. **INTERPRETATION AND CONCLUSION:** Midazolam 0.05 mg. kg⁻¹ as a co-induction agent with propofol 2.5 mg. kg⁻¹ is safe and effective in obtaining most favourable conditions for smooth insertion of laryngeal mask in children.

KEYWORDS: Co-induction, Midazolam, Propofol, Laryngeal mask airway.

INTRODUCTION: Propofol is a commonly used induction agent for insertion of laryngeal mask in children. When used as a sole agent, children require a larger dose of propofol for insertion of laryngeal mask airway than adults.^{1,2,4,5} This large dose needed for induction may be associated with haemodynamic and respiratory effects like hypotension,^{3,4} bradycardia, apnoea or hypoventilation.⁴ Midazolam when used in sub-anaesthetic doses reduces the dose of Propofol required for induction via a synergistic action.^{10,11} This practice of administering a small dose of sedative or other anaesthetic agent viz. midazolam, ketamine, propofol (auto co-induction), fentanyl, alfentanil to reduce the total dose of the induction agent is known as co-induction.¹⁰ It provides haemodynamic stability but has variable effect on recovery.

Hence, the present clinical study was undertaken to study the effectiveness of midazolam as co-induction agent with propofol in comparison to propofol alone for laryngeal mask insertion in children with objectives to assess:

1. The insertion characteristics for Laryngeal Mask Airway insertion.
2. The effectiveness of midazolam as a co-induction agent in lowering the induction dose of propofol and also in producing haemodynamic stability.
3. Recovery of the patient.

MATERIALS AND METHODS: This clinical study was undertaken at Cheluvamba Hospital attached to Mysore Medical College and Research Institute, Mysore during January 2009 to May 2010 after obtaining ethical committee clearance as well as informed consent from child's parents/guardian.

Sixty paediatric patients aged 3 years to 10 years of either sex belonging to ASA grade I and II undergoing elective short surgical procedures under general anaesthesia were included in the study. Patients aged less than 3 years or more than 10 years, those belonging to ASA grade III, IV, V and children with full stomach, allergy to egg or lignocaine, hyper reactive airway disease were criteria for exclusion. The subjects were allocated randomly into two groups with 30 patients in each.

Group I (n=30) – received i.v propofol 3.5 mg. kg⁻¹.

Group II (n=30) – received i.v midazolam 0.05 mg. kg⁻¹ two minutes prior to injection propofol 2.5 mg. kg⁻¹ i.v.

Pre anaesthetic evaluation was done on the evening before surgery and all the patients included in the study were pre medicated with Syrup Promethazine 0.3 mg. kg⁻¹ orally at bedtime. On the day of surgery, EMLA cream with occlusive dressing applied on the dorsum of both hands 1 hour before and child received no premedication.

On the arrival of the child in the operating room, a 22G intravenous cannula was inserted into the already identified peripheral vein and an infusion of isolyte P started. The patients were connected to multichannel monitor for heart rate, non-invasive blood pressure, oxygen saturation and continuous ECG monitoring.

ORIGINAL ARTICLE

The basal heart rate, blood pressure and oxygen saturation were recorded and children were pre oxygenated for 3 minutes via a facemask with either Jackson-Rees circuit (if child weighed <20kg) or Bain's circuit (if child weighed >20kg). Then anaesthesia was induced with propofol 3.5 mg. kg⁻¹ given i.v over 30 seconds in Group I or midazolam 0.05 mg. kg⁻¹ i.v, 2 minutes later, propofol 2.5 mg. kg⁻¹ given i.v over 30 seconds in Group II. The propofol dose was mixed with 1% lignocaine 0.5mg. kg⁻¹ to reduce the pain on injection. After another 30 seconds, the appropriate size laryngeal mask airway (#2 if child weighed 10-20kg, #2.5 if child weighed 20-30kg) with 2% lignocaine jelly applied on the dorsal aspect of the cuff was inserted as per standard insertion technique recommended by Brain. The cuff inflated, LMA was secured and the position confirmed by movements of the reservoir bag of the breathing circuit and bilateral equal chest expansion on gentle application of IPPV.

The insertion characteristics were compared among the two groups using:

- i. Mouth opening graded on three point scale:
 - Full (Fully relaxed jaw).
 - Partial (Some resistance).
 - Impossible.
- ii. Ease of laryngeal mask airway insertion graded on four point scale:
 - Easy (Placement at first attempt).
 - Some difficulty (Placement at second attempt).
 - Difficult (More than two attempts).
 - Impossible.

If failed on one attempt, a bolus of 0.5 mg. kg⁻¹ propofol was given. If impossible, use of LMA abandoned and alternative technique resorted.

Anaesthesia was maintained using 66% nitrous oxide and 33% oxygen, assisted if in apnoea or allowed to breathe spontaneously. No surgical or any other stimulus was applied during 5 minute study period. Then 0.5% to 1.5% halothane added which was withdrawn at closure and child allowed to breathe 100% oxygen at the end of surgery. Recovery was assessed and once the child was awake and breathing spontaneously with adequate tidal volume, thorough oral suctioning done and the laryngeal mask airway was removed. The child was observed for 30 min in the recovery room for any postoperative undesirable responses and then shifted to postoperative ward.

MONITORING: The insertion characteristics were noted using:

- Mouth opening graded on three point scale and
- Ease of insertion graded on four point scale.

These characteristics were compared between Group I and II.

The following hemodynamic parameters: Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Oxygen saturation (SPO₂) were recorded at basal, immediately after midazolam (co-induction agent) injection, zero minute – immediately after propofol injection, one, two, three, four, five minutes after propofol injection and the parameters compared within the group and between the groups.

ORIGINAL ARTICLE

The observations were statistically evaluated using Frequencies and Crosstabs, Independent Samples t-test, Paired Sample t-test and Repeated measure ANOVA:

- Hypotension was defined as >20% fall in SBP compared to basal value.
- Bradycardia was defined as HR <60 bpm.
- Duration of anaesthesia – from induction to removal of LMA.
- Duration of surgery – from surgical incision to closure.

RESULTS: The age, sex and weight distribution of the patients in two groups are comparable (Table 1) and $p > 0.05$. The type of surgery underwent by patients in both the groups are given in table 2.

The extent of mouth opening for LMA insertion after induction with the study drug (s) was full in 90% of patients in Group I and 93.3% of patients in Group II while partial mouth opening was observed in 10% and 6.7% in Group I and II respectively (Table 3). There was no statistically significant variation in mouth opening ($p > 0.05$). The ease of insertion of laryngeal mask airway was Easy in 90% in Group I and 100% in Group II, while some difficulty was encountered in 6.7% and was Difficult in 3.3% of patients in Group I ($p > 0.05$) (Table 4).

The haemodynamic parameters observed at various time intervals show that there was significant decrease in the mean value of each compared to its basal in both the groups while the fall was more gradual in Group II compared to Group I (Table 5) (Fig. 1, 2, 3, 4).

No undesirable response like coughing, gagging, laryngospasm or desaturation was encountered during insertion or removal of LMA in both the groups.

The mean duration of surgery was 15.6 minutes in Group I and 17.3 minutes in Group II while mean duration of anaesthesia was 24.8 minutes and 30.6 minutes in Group I and II respectively. There was no statistically significant difference in duration of surgery and anaesthesia between Group I and II ($p > 0.05$).

DISCUSSION: Allsop E et al¹¹ reported that in children aged 4-9yrs, it is safe and effective to insert a laryngeal mask airway immediately after induction of anaesthesia with propofol 3.5mg. kg⁻¹. Patel DK et al¹² found that propofol in a larger dose of 2.5-3.5 mg. kg⁻¹ is an effective induction agent in children aged 1-12yrs to achieve satisfactory anaesthesia in both premedicated and unpremedicated children. Saint-Maurice C et al¹³ reported that higher induction dose of propofol is required in children consistent with the larger value of V_{α} . In a study on children aged 3-12 yrs undergoing general anaesthesia for minor surgical procedures Martlew RA et al¹⁴ reported that premedication with oral midazolam 0.5 mg. kg⁻¹ 30-60 min before anaesthesia significantly shifted the propofol dose-response curve to left and the propofol dose requirements were reduced by one-third compared to unpremedicated children. The ED₅₀ of propofol for satisfactory laryngeal mask insertion was 3.8 (3.4-4.2) mg. kg⁻¹ and 2.6 (2.2-2.8) mg. kg⁻¹ in unpremedicated and premedicated children. Goel S et al⁴ employed propofol 3.5 mg. kg⁻¹ when used alone and propofol 2.5 mg. kg⁻¹ when either midazolam 0.05 mg. kg⁻¹ or ketamine 0.5 mg. kg⁻¹ was administered 2 min before propofol, both mixed with lignocaine 0.5 mg. kg⁻¹, and laryngeal mask inserted 30s after propofol injection in children aged 1-8yrs undergoing day-case surgery. They reported that the combination of propofol with midazolam or ketamine improved conditions for laryngeal mask insertion and produced stable haemodynamics. Similarly, in adults, Driver IK et al,¹⁵ Short TG et al¹ also reported that the propofol-midazolam

ORIGINAL ARTICLE

combination acts synergistically. Thus, in the present study, propofol 3.5 mg. kg⁻¹ was chosen as optimal dose in Group I while in Group II, midazolam was chosen as the co-induction agent and 0.05 mg. kg⁻¹ was administered 2 min before propofol 2.5 mg. kg⁻¹.

Driver IK et al,¹⁵ Driver I et al¹⁶ assessed the insertion characteristics 30s after propofol bolus and graded mouth opening on three point scale as full, partial and impossible, and ease of LMA insertion graded on four point scale as easy, some difficulty, difficult and impossible. Driver IK et al reported that the mouth opening was full in 100% and 70% while LMA insertion was easy in 100% and 93.3% in propofol-midazolam-alfentanil group and propofol group respectively. Similarly, Driver I et al reported that the mouth opening was full in 91% of the patients while LMA insertion was easy in 100% patients in propofol group. Goel S et al⁴ categorized the insertion characteristics 30s after propofol bolus as excellent, satisfactory and unsatisfactory depending on the relaxation of jaw, presence or absence of coughing, gagging, swallowing, limb movement and laryngeal spasm. They reported excellent insertion conditions in 27.8% and 44.4% of patients, satisfactory in 50% and 55.6% of patients and unsatisfactory in 22.2% and nil in propofol and propofol-midazolam groups respectively. Similarly, Martlew RA et al¹⁴ considered conditions for laryngeal mask insertion at 60s after propofol bolus as satisfactory or unsatisfactory. In present study, similar to Driver IK et al¹⁵ and Driver I et al,¹⁶ we assessed the insertion characteristics based on mouth opening and ease of insertion of laryngeal mask airway. The mouth opening was full in 90% and 93.3% of patients while partial in 10% and 6.7% of patients in Group I and II respectively. The insertion of LMA was easy in 90% of patients in Group I and 100% of patients in Group II while some difficulty was present in 6.7% of patients and was difficult in 3.3% of patients in Group I whereas some difficulty and difficult insertion were not present in Group II. Our findings were similar to that reported by Driver IK et al and Driver I et al. The Laryngeal Mask Airway insertion was easy in all 30 patients (100%) in Group II indicating significant improvement in insertion characteristics compared to Group I.

The decrease in mean HR was greatest at 3rd min (8.7%) in Group I and at 4th min (9.3%) in Group II, followed by return towards basal value during the study period. Thus, the decrease in mean HR in both the groups compared to its basal value was clinically significant (p<0.05). Our findings concur with the observations made by Goel S et al⁴ and Djaiani G et al¹⁷ who used midazolam as co-induction agent. The relative bradycardia in Group I compared to its basal reading was similar to observations made by Short SM et al,¹⁸ Hannallah RS et al² who used propofol as an induction agent.

The decrease in mean SBP was greatest at 2nd min in both the groups (10.3% and 8%), followed by return towards basal value during the study period. Thus, the decrease in mean SBP in both the groups compared to its basal value was clinically significant (p<0.05). Also the decrease in mean DBP and mean MAP in both the groups compared to its basal value was clinically significant (p<0.05). Our findings concur with the observations made by Goel S et al⁴ and Djaiani G et al¹⁷ who used midazolam as co-induction agent. Also similar to observations made by Short SM et al.¹⁸ Hannallah RS et al² and Djaiani G et al¹⁷ who used propofol as an induction agent.

In the present study, the undesirable responses- coughing, gagging, laryngospasm, desaturation were nil in both the groups, both at insertion and removal of LMA and findings concur with Driver IK et al¹⁵ observations in group propofol-midazolam-alfentanil.

The mean duration of surgery and anaesthesia were comparable (p>0.05), implicating no undue delay in recovery in Group II compared to Group I.

CONCLUSION: Midazolam as a co-induction agent in a dose of 0.05 mg. kg⁻¹ used with propofol 2.5 mg. kg⁻¹ is safe and effective in producing most favourable conditions for smooth insertion of laryngeal mask airway in children when compared to propofol 3.5 mg. kg⁻¹ administered alone. It did not produce haemodynamic instability and any undue delay in recovery. Hence, midazolam 0.05mg. kg⁻¹ as a co-induction agent along with propofol 2.5 mg. kg⁻¹ can be safely employed in paediatric patients for LMA insertion.

BIBLIOGRAPHY

1. Short TG, Chui PT. Propofol and midazolam acts synergistically in combination. *British Journal of Anaesthesia* 1991; 67: 539-45.
2. Hannallah RS, Baker SB, Casey WMB, McGill WA, Broadman LM, Norden JM. Propofol: Effective dose and induction characteristics in unpremedicated children. *Anesthesiology* 1991; 74: 217-9.
3. Mirakhur RK. Induction characteristics of propofol in children; comparison with thiopentone. *Anaesthesia* 1998; 43: 593-8.
4. Goel S, Bhardwaj N, Jain K. Efficacy of ketamine and midazolam as co-induction agents with propofol for laryngeal mask insertion in children. *Pediatric Anesthesia* 2008; 18: 628-34.
5. Srivastava U, Sharma N, Kumar A, Saxena S. Small dose propofol or ketamine as an alternative to midazolam co-induction to propofol. *Indian J. Anaesth.* 2006; 50 (2): 112-4.
6. Shah MX, Gandhi S, Chadha IA. Comparison of midazolam co-induction with propofol pre-dosing for induction of anaesthesia. *J Anaesth Clin Pharmacol* 2008; 24 (2): 197-200.
7. Kumar AA, Sanikop CS, Kotur PF. Effect of priming principle on the induction dose requirements of propofol- A randomized clinical trial. *Indian J. Anaesth* 2006; 50 (4): 283-7.
8. Anderson L, Robb H. A comparison of midazolam co-induction with propofol pre-dosing for induction of anaesthesia. *Anaesthesia* 1998; 53: 1117-29.
9. Amrein R, Hetzel W, Allen SR. Co-induction of anaesthesia: the rationale. *Eur J Anaesthesiol Suppl.* 1995; 12: 5-11.
10. Stoelting RK, Hillier SC. *Pharmacology and physiology in anaesthetic practice.* 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. pp. 140-7, 155-63.
11. Allsop E, Innes P, Jackson M, Cunliffe M. Dose of propofol required to insert the laryngeal mask airway in children. *Pediatric Anesthesia* 1994; 5: 47-51.
12. Patel DK, Keeling PA, Newman GB, Radford P. Induction dose of propofol in children. *Anaesthesia* 1988; 43: 949-52.
13. Saint-Maurice C, Cockshott ID, Douglas J, Richard MO, Harmey JL. Pharmacokinetics of propofol in young children after a single dose. *Br. J. Anaesth* 1989; 63: 667-70.
14. Martlew RA, Meakin G, Wadsworth R, Sharples A, Baker RD. Dose of propofol for laryngeal mask airway insertion in children; effect of premedication with midazolam. *Br. J. Anaesth* 1996; 76: 308-9.
15. Driver IK, Wiltshire S, Mills P, Lillywhite N, Howard-Griffin R. Midazolam co-induction and laryngeal mask insertion. *Anaesthesia* 1996; 51: 782-4.
16. Driver I, Wilson C, Wiltshire S, Mills P, Howard-Griffin R. Co-induction and laryngeal mask insertion. A comparison of thiopentone versus propofol. *Anaesthesia* 1997; 52: 695-703.

ORIGINAL ARTICLE

17. Djaiani G, Ribes Pastor MP. Propofol auto-co-induction as an alternative to midazolam co-induction for ambulatory surgery. *Anaesthesia* 1999; 54: 63-7.
18. Short SM, Aun CST. Haemodynamic effects of propofol in children. *Anaesthesia* 1991; 46: 783-5.

Demographic data	Group I (n=30)	Group II (n=30)
Gender (Male/Female)*	76. 7 / 23. 3	80 / 20
Age (years)	6. 9 (2. 36)	7. 3 (2. 47)
Weight (kilograms)	18. 7 (5. 43)	18. 0 (5. 67)

Table 1: Demographic data

*Value in %, rest all mean (SD)

Sl. No.	Type of Surgery	GROUP I n=30	GROUP II n=30
1	Herniotomy and Hydrocoel disconnection	18	14
2	Orchidopexy	3	4
3	Circumcision	6	7
4	Rectal polyp excision	2	1
5	Epigastric hernia	1	1
6	Umbilical hernia	-	1
7	Appendicectomy	-	1
8	SSG (Leg Rt.)	-	1

Table 2: Showing type of surgical procedures

Scale	GROUP I n (%)	GROUP II n (%)
Full	27 (90)	28 (93. 3)
Partial	3 (10)	2 (6. 7)
Impossible	0	0

Table 3: Extent of Mouth opening for LMA Insertion

Scale	GROUP I n (%)	GROUP II n (%)
Easy	27 (90)	30 (100)
Some difficulty	2 (6. 7)	0
Difficult	1 (3. 3)	0
Impossible	0	0

Table 4: Showing Ease of Insertion of Laryngeal Mask Airway

ORIGINAL ARTICLE

Time interval	Mean HR (bpm)		Mean SBP (mmHg)	
	GROUP I	GROUP II	GROUP I	GROUP II
Basal	122.63±14.31	121.73±22.95	113.40±13.59	116.96±14.12
Midazolam	-	119.80±21.77	-	118.23±13.36
Propofol (0 min)	120.53±17.75	116.80±22.35	109.90±14.19	115.10±12.17
1 min	114.73±20.29	114.30±22.38	107.66±16.76	109.26±13.82
2 min	112.60±18.29	114.10±23.53	101.76±14.13	107.66±14.41
3 min	112.00±16.99	112.60±21.17	103.90±10.82	107.90±15.61
4 min	114.13±17.13	110.53±19.83	105.06±10.42	109.96±11.53
5 min	113.33±17.89	110.93±17.74	105.66±10.97	111.16±10.19

Table 5: Showing changes in mean heart rate and mean systolic blood pressure

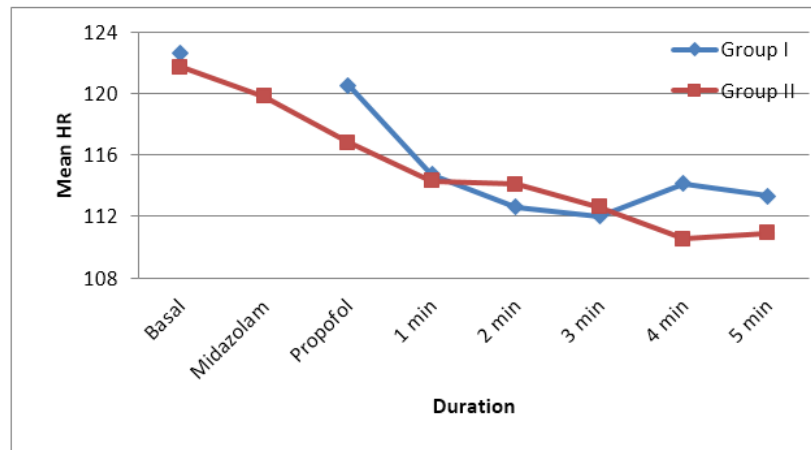


Fig. 1

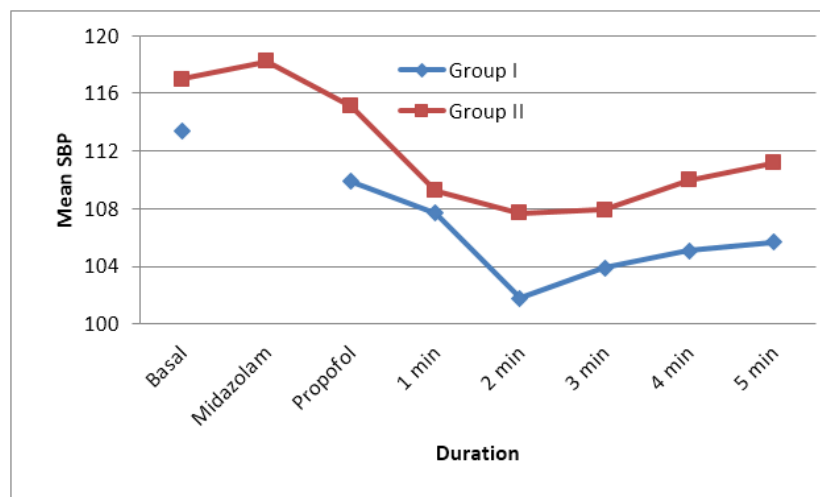


Fig. 2

ORIGINAL ARTICLE

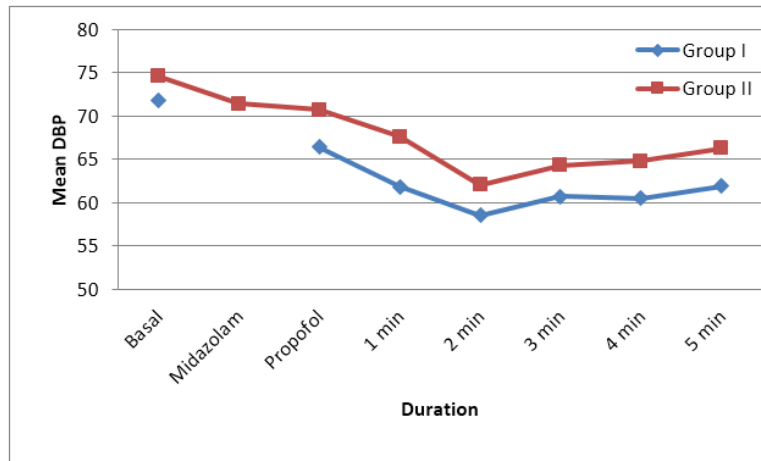


Fig. 3

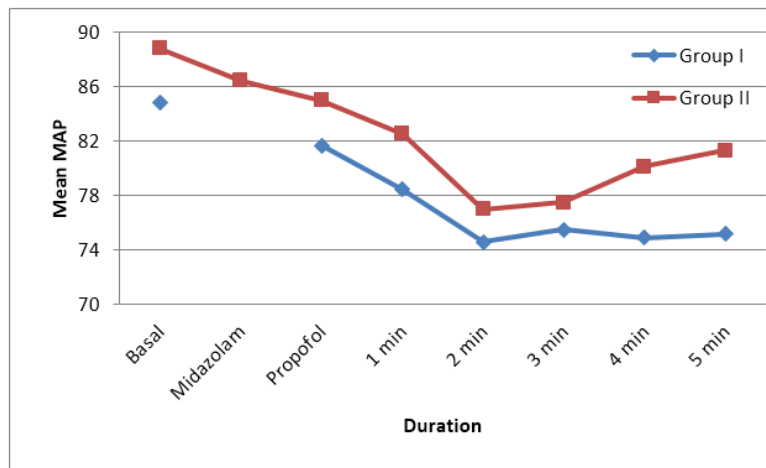


Fig. 4

AUTHORS:

1. Ashwini S.
2. Kempachary

PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Anaesthesiology, Shivamogga Institute of Medical Sciences, Shivamogga, Karnataka.
2. Professor, Department of Anaesthesiology, Mysore Medical College & Research Institute, Mysore, Karnataka.

FINANCIAL OR OTHER

COMPETING INTERESTS: None

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Ashwini S,
No. 64, Sri Renuka Nilaya,
1st Cross, Channappa Layout,
Shivamogga-577201.
E-mail: ashwini.satrasala@gmail.com

Date of Submission: 12/03/2015.
Date of Peer Review: 13/03/2015.
Date of Acceptance: 16/03/2015.
Date of Publishing: 24/03/2015.