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Original Research Article

Effective dose of propofol for smooth induction in midazolam premedicated and in unpremedicated children

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ABSTRACT

Background: Propofol, an intravenous (IV) anaesthetic agent, is widely used in paediatric day care surgeries. Present study was conducted to determine clinically effective dose of Propofol for smooth induction in children.
Methods: This randomized controlled study was conducted in 100 children of American Society of Anaesthesia (ASA) grade I and II, posted for short genitourinary surgeries. Group P patients received premedication with injection glycopyrrolate and midazolam IV. Group U patients were unpremedicated. Both groups were split in five subgroups with ten patients in each as per propofol dose of 2.0, 2.5, 3.0, 3.5, and 4.0mgkg^{-1} respectively. Following observations were made-pain on injection site, facemask tolerance, repeat dose and total dose of Propofol required for smooth induction, time of recovery and complications like post-operative nausea and vomiting (PONV). All data was analyzed by using chi square test and student t test.
Results: Demographic profile showed no significant difference. Mean dose of Propofol in group P was 3.29±0.51 mg kg^{-1} while for group U was 3.70±0.57mg kg^{-1}. Facemask tolerance was maximum in group P5 (100%) followed by (80%) in U5. Mean dose of Propofol required for younger children 1-3 years (group P 3.46±0.43 mgkg^{-1} v/s group U 3.94±0.48 mgkg^{-1}) was much higher than dose required for 7-10 years (group P 3.13±0.52 mgkg^{-1} and group U 3.18±0.59 mgkg^{-1}) for both groups. Recovery time after anaesthesia was delayed in group P and complications were more in group U.
Conclusions: Propofol is the drug of choice for paeditric ambulatory surgery. Midazolam premedication enhances the benefits.

Keywords: Ambulatory surgical procedures, Midazolam, Postoperative nausea and vomiting, Propofol

INTRODUCTION

Propofol (ICI 35868) is an IV anaesthetic agent with hypnotic, sedative, and amenestic properties, which cause loss of consciousness reliably and rapidly. It is considered as first choice drug for day care surgeries due to short elimination half-life, high plasma clearance, and intrinsic anti emetic features.[1] Desirable features of Propofol include smooth and rapid onset of induction, easily controlled maintenance, minimal excitatory events, rapid and clear-headed recovery, minimum PONV, no emergence reaction, or dysphoria.[2] The major drawback of propofol is pain at injection site, which can be minimized by pre-treatment with lignocaine or mixing lignocaine with propofol and choosing anticubital fossa vein instead of small veins on the dorsum of hand.[3,4] Other disadvantages includes haemodynamic and respiratory depression and unavailability of any antagonistic drug.[5] Pharmacokinetic changes influence dose requirement in children and adults, children require a relatively larger induction dose of propofol than adults.[6] Synergistic effect of propofol and midazolam is seen, as

both interact on Gamma-Amino Butyric Acid (GABA) receptors, which significantly reduces propofol dose requirement.[7]

Nicoll in 1900's gave concept of ambulatory surgery and anaesthesia.[8] Paediatric day care surgery is the demand of present era of anaesthesia as it is cost effective, reduces hospitalization time and feeding schedule is less disturbed. Thus, the need for anaesthetic agent arises which provides stable haemodynamics, good analgesia, rapid recovery, early ambulation and minimal complications.[9] Propofol is considered as an anaesthetic agent of choice.

The present study was carried out in paediatric patients posted for short surgical procedures. The primary objectives of the study were to determine clinically effective dose of propofol for smooth induction in children (1-10 years) who were pre medicated with Midazolam as well as in unpremedicated children, which was observed by facemask tolerance. Secondary aims were to observe pain on injection site, recovery time, and PONV.

METHODS

This randomized controlled study was conducted in paediatric tertiary care hospital. Approval from institutional ethical committee was taken. Written informed consent was obtained from each patient's parents or guardians. After statistical power analysis taking into account parameter of facemask tolerance and in consultation with statistician to get power of study >85%, 100 children of ASA physical status I and II, age group one to ten years of either sex posted for planned short surgical procedures like herniotomy, urethroplasty and orchidopexy on day care basis, were included in this study. Exclusion criteria were ASA grade III and IV, patients manifesting any systemic illness and hypersensitivity to any drug or food.

Patients were randomly divided in two groups of fifty patients each. Group P patients received premedication five min before induction with injection Glycopyrrolate 0.008 mg kg^{-1} and injection Midazolam 0.04 mg kg^{-1} IV. Group U patients were unpremedicated. Both groups were further split in five subgroups with ten patients each according to the induction dose of Propofol allocated likewise 2.0, 2.5, 3.0, 3.5, and 4.0mgkg^{-1}. Every child was prescreened in detail one day before procedure.

History, general physical examination, and airway evaluation were conducted. Haemogram, coagulation profile, and routine urine examination were done in all children. Patients were kept nil orally for 4-8 hours prior to anaesthesia. Eutectic mixture of local anaesthetics (EMLA) cream was applied in anticubital fossa vein of each child about 45 min before insertion of IV cannula and covered with sterile dressing.

In operation theatre monitors were attached and base line parameters like electrocardiogram (ECG), heart rate (HR) and pulse oximetry (SpO_2) were monitored and noted down. IV cannula was secured and IV fluid was started. To avoid pain on injection site 0.5ml of 2% Lignocaine was added in 20 ml of Propofol (1%) and used in 30 min of preparation. Propofol injection was given IV slowly for 30 seconds, dose as per allocated sub group. Patients were ventilated by using appropriate sized facemask with 100% oxygen, if needed jaw was lifted to maintain the airway. Quality of tolerance of facemask was noted and graded as Excellent-no body movements, no discomfort on lifting jaw. Good-no body movements but little discomfort on lifting jaw. Fair -patient accepted facemask with little body movement and showed struggle on lifting jaw. Non-tolerance-patient showed gross body movements and struggled to remove facemask. Poor responders were given Propofol in incremental doses of 5ml in each bolus until the tolerance for facemask was achieved.

After checking adequacy of ventilation via facemask, injection succinyl choline 2mgkg^{-1} was given and endotracheal intubation done with appropriate size polyvinyl chloride (PVC) endotracheal tube. Maintenance of anaesthesia was done by oxygen and nitrous oxide (O_2:N_2O) in ratio of 40:60 and halothane inhalation (0.2-0.6%) intermittently. Muscle relaxation was achieved with injection atracurium 0.5mgkg^{-1} as loading dose and there after 0.05mgkg^{-1} as maintenance dose. Diclofenac suppository (0.5mgkg^{-1}) was inserted per rectum.

After completion of surgery, anaesthesia was reversed with injection Neostigmine 0.05mg/kg and injection Glycopyrrolate. Patient was extubated after adequate oral-pharyngeal suction in supine position. Time of recovery was taken after reversal of anaesthesia until the time taken for opening of eyes, cry/protrusion of tongue, limb movements, orientation, and verbal communication. Orientation was judged by asking questions like name, time, name of parents, date etc according to the age of child. In small children (1-3 years) smile on identifying parents or approach of hand for familiar things was noted down.

Following observations were made from induction to recovery-pain on injection site, facemask tolerance, repeat dose, and total dose of Propofol required for smooth induction, duration of surgery, time of recovery, and PONV. We considered facial expression of pain, withdrawal of hand, cry, and verbal complains of pain, as pain on injection of Propofol.

Statistical analysis

All data was statistically analyzed by applying chi-square tests. Data were noted in mean ±SD and *p* value of <0.05 considered significant. To see the differences between the two groups student's t test was used.

RESULTS

Demographic profile of patients in both the groups in this study showed no significant difference in relation to age, weight and sex. (p >0.05) However, both groups showed male preponderance (Table 1).

Table 1: Demographic profile.

	Group P	Group U	P value
Age (years)			
Mean ±SD	4.20±2.87	4.23±2.91	>0.05 NS
Weight (kg)			
Mean ±SD	13.70±5.04	13.97±5.62	>0.05 NS
Sex			
Female:Male	5:45	2:48	

NS- Not significant

Mean dose of Propofol in group P was found to be 3.29±0.51mgkg^{-1} while for group U was 3.70±0.57mgkg^{-1}. The difference was statistically significant (p value <0.05).

The mean dose of Propofol in subgroup P1 was 2.75±0.40mgkg^{-1} and in U1 3.27±0.57mgkg^{-1}, P2-2.93±0.48mgkg^{-1} and U2-3.72±0.53mgkg^{-1}, P3-3.18±0.24mgkg^{-1} and U3-3.41±0.44mgkg^{-1} (p value <0.05 significant). There were statistically significant differences in mean dose in between two groups until subgroups 3 (3.0mgkg^{-1}). The difference between subgroups 4 and 5 was not significant (p value >0.05); 3.60±0.21mgkg^{-1} and 3.87±0.47mgkg^{-1} being the doses in subgroups P4 and U4 respectively; 4.00±00mgkg^{-1}and 4.25±0.33mgkg^{-1} in P5 and U5 respectively. The group U required more incremental doses of Propofol in each subgroup as compared to group P (Table 2).

Table 2: Mean doses as per subgroups.

Group P	Mean dose mg kg^{-1}	Facemask Tolerance	Group U	Mean dose mg kg^{-1}	Facemask Tolerance	p value (mean dose)
P-1	2.75±0.40	20%	U-1	3.27±0.57	10%	<0.05 significant
P-2	2.93±0.48	50%	U-2	3.72±0.53	10%	<0.05 significant
P-3	3.18±0.24	60%	U-3	3.41±0.44	50%	<0.05 significant
P-4	3.60±0.21	80%	U-4	3.87±0.47	60%	>0.05 insignificant
P-5	4.00±00	100%	U-5	4.25±0.33	80%	>0.05 insignificant
Mean dose	3.29±0.51		Mean dose	3.70±0.57		<0.05 significant

Facemask tolerance in both groups was taken as criteria for calculating mean induction dose of Propofol in each subgroup. We observed that tolerance to face mask was lesser in subgroup 1 (P1/U1) of both groups. Only 20% of children in subgroup P1 and 10% in U1 could tolerate the facemask. As the dose range increased the facemask tolerance improved. In the premedicated subgroups P2-P5, it was 50%, 60% 80% and 100% respectively, while for unpremedicated subgroups U2-U5 the percentage of children who could tolerate facemask with the given dose range was 10%, 50% 60% and 80% respectively.

Unpremedicated patients required more dose than premedicated children for good facemask tolerance. Even dose of 3.5mgkg^{-1} was seen to be insufficient to tolerate facemask smoothly in group U children. Group P children required lesser dose than group U for good tolerance of facemask (Table 2).

There was significant (p <0.05) difference in mean dose between both groups in the age group 1-3 years and 3.5-5 years. These differences were insignificant (p value >0.05) in older children 5.5-10 years.

In our study, we noted that smaller children required more induction dose of Propofol than older children did, whether premedicated or not.

In 1-3 years age group mean induction dose in group P was 3.46±0.43mgkg^{-1} and in group U 3.94±0.48mgkg^{-1}. In age group 3.5-5 years mean dose required for group P was 3.20±0.61mgkg^{-1} and for group U was 3.79±0.52mgkg^{-1}. The difference of mean doses in these age groups were significant (p value <0.05).

In age group 5.5-7 years, mean dose in group P was 3.13±0.79mgkg^{-1} and in group U was 3.34±0.48mgkg^{-1}. In age group 7.5-10 years group P children needed 3.13±0.52mgkg^{-1} as compared to group U who needed 3.18±0.59mgkg^{-1}. These differences in mean dose of Propofol were found to be insignificant (p value >0.05) (Table 3).

Table 3: Mean dose as per age groups.

Age group (yrs)	Group P (mg kg^{-1})	Group U (mg kg^{-1})	p value	
1-3 years	3.46±0.43	3.94±0.48	<0.05	Significant
3.5-5 years	3.20±0.61	3.79±0.52	<0.05	Significant
5.5-7 years	3.13±0.79	3.34±0.48	>0.05	insignificant
7.5-10 years	3.13±0.52	3.18±0.59	>0.05	insignificant

Recovery profile in both groups showed significant difference though duration of surgery was similar for both groups. Time of recovery taken after discontinuation

of anaesthesia for eye opening in group P was 2.43±0.38 min and in group U was 1.74±0.83 min. For cry /protrusion of tongue, time taken was noted down to be 4.59±0.51 min in group P as compared to 3.90±0.37min in group U. Orientation time was 7.14±0.64 min and 6.12±0.48 min for group P and U respectively. This difference in time taken for eye opening, cry/ protrusion of tongue and orientation was statistically significant with p value <0.05 for each criterion. Recovery time was earlier for unpremedicated children (Table 4).

Table 4: Complications and recovery time.

	Pain on injection		PONV		Recovery time (min ±SD)		
	No.	%	No.	%	Eye opening	Cry/ protrusion of tongue	Orientation
Group P	11	22%	4	8%	2.43±0.38	4.59±0.51	7.14±0.64
Group U	13	26%	7	14%	1.74±0.83	3.90±0.37	6.12±0.48
p value					<0.05 significant	<0.05 significant	<0.05 significant

Complications during and after induction were observed in both groups. We found that complications occurred more in unpremedicated children. In group P, 11 out of 50 patients (22%) complained of pain on injection while this incidence in group U was 13 out of 50 children (26%). PONV incidences were also more in unpremedicated patients; seven (14%) as compared to premedicated patients; four (8%) (Table 4).

DISCUSSION

Propofol shows a variety of responses in perioperative period. Thus, doses need to be titrated according to the individual need. Factors, which influence dose requirement, include age, weight, pre-existing medical conditions and type of surgical procedures. Children of different age group produce different responses to Propofol. In addition, children need more Propofol for induction and maintenance of anaesthesia than adults.[10]

This study was undertaken to ascertain optimal induction dose of Propofol in children taking into consideration smooth induction, rapid recovery, and side effects. We considered age, weight and sex as parameters of demographic profile of patients. The difference between two groups was not significant (p >0.05). Our selection of age group, weight and sex distribution in this study correlates with study of D K Patel et al and, Smith et al.[11-12] In paediatric ambulatory surgeries the frequency of genitor urinary surgeries are more and there is always male preponderance in these types of studies. We selected children posted for genito-urinary short procedures like herniotomy, orchidopexy, and urethrolasty to keep the surgical conditions identical in urethroplasty both groups.

In this study injection glycopyrrolate 0.008mgkg^{-1} and injection midazolam 0.04mgkg^{-1} were given IV as premedicants in group P patients, while group U children were not given any premedication. Glycopyrrolate was chosen over Atropine due to cardio stability, less tachycardia, potent antisialogogue action and lesser increase in body temperature.[13] Midazolam was used prior to administration of Propofol to reduce its dose and minimize the side effects. This phenomenon is referred to as co-induction.[14] The objective is to improve the ratio of desired effect v/s adverse effects. In addition, it leads to reduction of cost of induction agent.[15]

In our study mean dose of propofol in group P was 3.29±0.51mgkg^{-1} while it was 3.70±0.57 mg kg^{-1} in group U. The difference in mean dose in both groups was significant (p <0.05) which could be due to midazolam premedication in group P. Our results co-relate with studies by various authors. One study has proved that midazolam decrease induction dose of propofol by 23%.[16] In a recent study by Adnan M et al, it was found that midazolam decreases the dose of Propofol from 5mgkg^{-1} to 4mgkg^{-1} with effective anaesthesia in 100% patients and lower incidence of adverse effects like coughing, limb movements and incomplete jaw relaxation during LMA insertion.[17] Short and Chiu et al, also suggested reduction in propofol dose by 52% when using midazolam along with propofol.[18] Bhaskar P et al, have echoed similar results. [19]

Different authors have used various parameters to assess the end point of injecting IV anaesthetic agents, like loss of eye lash or corneal reflexes, response to squeezing of trapezius muscle, cessation of counting, acceptance of facemask etc.[20,21] Most commonly used end point in paediatric patients are loss of eyelash reflex and facemask acceptance.[11,22,23] However, loss of eyelash reflex may not be observed while using large doses of propofol.[24] Thus, acceptance of facemask has been used in our study as end point of induction with Propofol.

In this study maximum tolerance of facemask (100%) in group P was seen with dose 4.0mgkg^{-1}, propofol (P5) while in group U (80%) of children tolerated facemask using propofol in dose of 4.25±0.33mgkg^{-1} (U5). Subgroups P-1, P-2, P-3, P-4 showed 20%,50%,60%, and 80% facemask tolerance as compared to 10%,10%,50% and 60% in subgroups U-1, U-2, U-3, U-4 respectively.

This showed that facemask tolerance was better at lower dose range in premedicated subgroups as compared to unpremedicated subgroups. Our results coincide with various other studies like Patel DK et al, Manschott et al.[11,25] DK Patel et al, concluded in their study that 4.3mgkg^{-1} propofol was required for facemask tolerance in premedicated children as compared to dose of 5.2mgkg^{-1} for unpremedicated children. They had used trimperazine 3.0mgkg^{-1} for premedication.[11] Similarly Manschott et al, concluded that 2.5mgkg^{-1} propofol if preceded by 5µgmkg^{-1} alfentanil was appropriate induction dose of propofol in children of age 3-15 years.[25] Hanallah et al, recommended induction dose of propofol as 2.5-3mgkg^{-1} for unpremedicated children of age group 3-12 years.[22] Westrin P et al, also reported Propofol dose for satisfactory induction in 50% unpremedicated infants (1-6 months) to be 3.8±0.2mgkg^{-1} and for children (8-12 years) to be 2.7±0.1mgkg^{-1}.[24]

We also compared mean dose of propofol as per the age groups, we found that mean dose of propofol reduced from 3.46±0.43mgkg^{-1} (1-3 years) to 3.13±0.52mgkg^{-1} (7.5-10 years) in premedicated group. Similarly, dose decreased from 3.94±0.48mgkg^{-1} to 3.18±0.59mgkg^{-1} in unpremedicated group. The difference in mean dose was significant (p <0.05) between two groups up to 5 years of age, which became non-significant (p >0.05) thereafter. Our findings coincide with various studies available in literature.[3,11,13,22,24-26] In a study by Steur et al, on 2271 children, divided in age groups as <3 months, 3-6 months, 6-12 months and 1-3 years, they observed that relatively more dose of propofol was required in youngest age group than older patients.[27]

We also observed mean time taken for recovery from anaesthesia. We took criteria like eye opening, cry/protrusion of tongue and orientation in children of both groups. The mean time taken for eye opening, cry/protrusion of tongue and orientation for group P was as 2.43 ±0.38 min, 4.59±0.51 min, and 7.14±0.64 min respectively. Similarly, values for these parameters for group U children were 1.74±0.83 min, 3.90± 0.37 min, and 6.12±0.48 min respectively. The differences in values of both groups were found to be significant (p value <0.05). Our results are in concordance with Elwood T et al, who showed that premedication with Midazolam delayed the time for eye opening after anaesthesia but does not delay time of discharge after anaesthesia.[28] Similarly, Viitanen H et al conducted their study in 1-3 years old children, posted for adenoidectomy. They concluded that emergence and early recovery was delayed after oral midazolam as premedication with no change in discharge time after induction of anaesthesia with propofol and maintenance with sevoflurane.[7] Various other studies in this respect also correspond to our observations.[13,26,29,30]

Pain on injection with Propofol was also observed in our study. Kay and Rolley et al in 1977 commented that pain on injection is the commonest complaint by patients after Propofol injection.[31] A 85% of children experience pain after Propofol injection, with higher incidence in younger children.[32,33] Incidence of pain varies 4%-30 % according to authors, which depend on factors like size and site of vein, speed of injection, dilution, temperature of injection solution and concomitant drugs like local anaesthetics, Ketamine,opiods, and non steroidal anti-inflammatory drugs(NSAID).[3,11,22,23,34,35]

Hanallah et al, observed that 6.6% moderate pain on injection was experienced in children with Propofol if antecubital fossa veins were used.[22] Scott et al, also pointed out that causation of pain is affected by size of vein.[36] Pretreatment with lignocaine, mixing lignocaine with propofol and using alfentanil 5µgmkg^{-1} as premedication has been used in various studies to alleviate pain with Propofol injection.[25,35,37]

In our study, 22% of group P children (11 out of 50) and 26% of group U children (13 out of 50) experienced pain on injection with propofol. We used 0.5ml of 2% lignocaine mixed with 20 ml of 1% propofol solution to reduce pain on injection. We noted that younger children (1-3 years) had more incidences of pain than older children did. This could be due to small sized veins in younger children. Our results coincide with studies by various authors.[3,11]

PONV was noted down in our study from end of anaesthesia until 12 hours post operatively. Incidence of PONV in group P was found to be 8% (4 out of 50) whereas in group U it was 14% (7 out of 50). Most of the children showing nausea and vomiting were unpremedicated, older and had undergone orchidopexy or inguinal hernia repair.

Our results correlate with study by Patel DK et al who found incidence of PONV in their study to be 7.7%.[11] Authors have stated that rate of PONV in children aged 3 years or above can be almost twice as in adults .[38] The risk of PONV is very low in children less than 2 years of age.[39] Studies have shown that low dose intra operative Propofol infusion or bolus reduces PONV itself or in combination with other antiemetic.[40,41] Apfel et al, found 19% incidence of PONV with use of propofol. Society of ambulatory surgery has provided guidelines for management of PONV (2014) in which they have recommended regional anaesthesia or total intravenous anaesthesia (TIVA) with Propofol in high-risk patients for PONV.[42,43]

CONCLUSION

Propofol is a drug of choice for paediatric ambulatory surgery. Smooth induction, fast and uncomplicated recovery and minimal emetic sequelae are assets of Propofol induction in children, when used in optimal doses. These benefits are enhanced by premedication with Midazolam. However, pain on injection limits the use of propofol in children. Addition of lignocaine and

using antecubital fossa veins are helpful for its alleviation.

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