Comparative Evaluation of Safety and Efficacy of Clear Solution of Propofol and Emulsion of Propofol During Induction, Maintenance and Recovery for Various Surgical Procedures

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Abstract

Purpose: The purpose of the study was to compare efficacy of two different preparations of propofol (Emulsion and clear solution) during anesthesia.

Method :The study was conducted in 50 patients of ASA Grade I / II of either sex in age group of 16-40 yrs. After taking informed consent the patients were randomized into two equal groups: In group I induction and maintenance of anaesthesia with propofol emulsion and in group II clear solution of propofol was used.

Results: No significant difference in the total doses of propofol, required for induction and maintenance of anaesthesia in the groups. The incidence of pain on injection is more in group II.

Conclusion: Clear solution of propofol is an equally efficacious alternative to its emulsion preparation. Clear solution is lipid free, easily stored, and can be repeatedly withdrawn from the vial without risk of bacterial contamination. Pain at the injection site was the only drawback .

INTRODUCTION

The development of anaesthesia since its introduction in 1846 has been erratic, long periods of stagnation occasionally broken by improvements and advances. Anesthesia as we know it today was first used by W.T.G. Morton of Boston in the U.S., who gave ether at Massachusetts General Hospital on 16 October, 1846.

Before the 1930s, the anaesthetists administered one or two volatile agents to produce unconsciousness, muscle relaxation and deafferentation. This gave place to various techniques of the so called “balanced anaesthesia” and so the amount of toxic drugs to which the patients were exposed was reduced and the hazards of general anaesthesia became less. Intravenous drugs then appeared on the scene.

Inhalation agents have the advantage of rapid onset and offset of action and the anaesthesiologist has the ability to exercise control over its concentration by simple adjustment of vapourizer dial.

In early 1930s, intravenous barbiturates were used for induction of anaesthesia. Propofol then came into use. Its first reported use was in 1977. It has rapidly gained immense popularity and has become established as a serious rival to thiopentone. Propofol offers:-rapid onset of action, easily controllable depth of anaesthesia, rapid metabolism without accumulation, speedy and complete recovery, minimal PONV, safety in malignant hyperpyrexia, reduction of theatre pollution.[1,2]

The technique of intravenous anaesthesia is developing

continuously and has reached a stage where anaesthesiologist are enthusiastically using intravenous anaesthetics both for induction and maintenance of anaesthesia and thus maintaining the “triad of anaesthesia” i.e. amnesia, analgesia and muscle relaxation by total intravenous drugs, short-acting opioids and muscle

Although, Propofol has many pharmacokinetic advantages over other induction agents (Thiopentone, Ketamine), its emulsion base has certain drawbacks like lipid overload, bacterial contamination, increased risk of postoperative infections, increased risk of external contamination on repeated withdrawal from the vial.[3,4]

An agent with the advantages of propofol but without the drawbacks has long been awaited. Recently, a clear solution of Propofol has been introduced. Advantages of clear solution of Propofol: Stable at room temperature, withdrawn from vial repeatedly, non toxic and safe for i.v. administration, equipotent to emulsion preparation ,no lipid overload and free of soyabean and egg lecithin, no risk of postoperative infections, no risk of external contamination, economical as it can be dispensed again and again.

The clear solution of propofol is presently in Phase III trials. We compared the clear solution and the emulsion with regards to their efficacy.

METHODS

The study was conducted in 50 patients of ASA Grade I and II of either sex in the age group of 16-40 yrs .All patients scheduled for the various surgical procedures underwent thorough pre-anaesthetic check up and investigations to rule out any systemic involvement other than those indicated for surgical procedure. After taking informed consent, the patients were allocated randomly into two equal groups:

Group I- induction of anaesthesia with intravenous propofol emulsion 2-2.5 mg/kg, i.v. fentanyl 1.5 mcg/kg and i.v Vecuronium 0.08-0.1 mg/kg for facilitation of intubation.

Group II-patients of Gp II induced with i.v. clear solution of propofol 2-2.5 mg/kg, i.v. fentanyl l-1.5 mcg/kg and i.v. vecuronium 0.08-0.1 mg/kg for facilitation of intubation.

In Group I patients, infusion of emulsion of propofol 1% (10 mg/cc in 50 cc syringe), fentanyl (2 mcg/cc in 50 cc) were prepared and fitted in two separate infusion pumps and connected with extension lines.

In Group II patients infusion of clear solution of propofol 1% (10 mg/cc in 50 cc syringe), fentanyl (2 mcg/cc in 50 cc syringe) were prepared and fitted in two separate infusion pumps and connected with extension lines.

IN BOTH THE GROUPS

After overnight fasting, the patients were shifted inside premedication room. After assessment of baseline haemodynamic parameters, patients were premedicated with intra-muscular Glycopyrrolate 0.2 mg 30 minutes before surgery.

After shifting inside the operation theatre, intravenous line with 18 gauge cannula were established in upper limbs. The multi channel H-P monitor was installed for pulse, blood pressure heart rate, ECG, andSpO_2 monitoring.

The baseline haemodynamic parameters were recorded. After pre-oxygenation for 5 min, all patients were induced with i.v. propofol (Group I- emulsion of propofol, Group II- clear solution of propofol) 2-2.5 mg/kg (till loss of eyelash reflex), fentanyl 1.5 mcg/kg and endotracheal intubation was facilitated by i.v. vecuronium 0.08-0.1 mg/kg and IPPV was started. After induction, all the patients were given loading doses of propofol 1 mg/kg IV and IV vecuronium 0.1 mg/kg.

Groups I patients (Using emulsion of propofol for induction and maintenance) anaesthetic triad was maintained by continuous infusion of emulsion of propofol @ 6 mg/kg/hr, N2O: O2 : : 50 : 50, continuous infusion of fentanyl 1 mcg/kg/hr for analgesia and for muscle relaxation i.v. vecuronium as bolus as per requirement assessed by the above mentioned criteria of haemodynamic variability, PSRT score and clinical sign of adequate muscle relaxationWhile in group II patients clear solution of propofol was used for induction and maintenance.

The rate of infusion was titrated both according to the individual patient's requirements and varying levels of surgical stimulations.

Throughout the intra operative period boluses were also kept ready for both the groups to meet any abrupt increase in surgical stimulation that is skin incision, peritoneal traction, bowel and visceral handling etc which cannot be managed just by increasing the rates of infusions.

In both the groups ventilation was controlled to keep the ETCO2 between 35-40 mm Hg and SpO2 between 95-100%. The sequence of terminating infusions or

switching of infusion pumps in both the groups was according to the "Context sensitive half life" of individual drugs .The infusion of fentanyl was stopped 15-20 min , before and propofol 5-10 min before the end of surgery .

At the end of surgery, the residual neuromuscular paralysis was reversed by glycopyrrolate 10 mcg/kg i.v. and neostigmine 0.05 mg/kg i.v. in all patients. Patients were extubated on table. Emergence and recovery from anaesthesia and recovery score were assessed.

STATISTICAL ANALYSIS

The results were analyzed using the t-test to find out if the differences observed between the two groups were statistically significant.

RESULTS

The study was conducted in 50 patients of ASA Grade I and II of either sex in the age group of 16-40 yrs .All patients scheduled for the various surgical procedures underwent thorough pre-anaesthetic check up and investigations to rule out any systemic involvement other than those indicated for surgical procedure. After taking informed consent, the patients were allocated randomly into two equal groups. We recorded the following observations from our study -

With Propofol emulsion (group I) the average induction time was 68.14±1.26 sec, the average dose was 2.5±0.23 mg/kg. 86% patients had Grade I and 14% had grade II quality of induction as shown in tables 3, 4, 5. The induction dose in our study was given over 20 seconds.

In group II the average induction time was 72.21±1.21sec, the average dose of induction was 2.245±0.23mg/kg. 88% pts had Grade I and 12% had grade II induction.

During recovery, the average time of eye opening in group I was 9.68 ± 1.38min and that of group II was 10.48± 1.36min in our study as shown in table 4.

Average time at which patients get oriented was as follows- Group I-19.1± 1.91min, Group II- 18.6±2.91sec in our study as shown in table 4. The average time at which patients are able to sit independently was- Group I -32.3± 2.31min, Group II– 30.1±2.32 min in our study as shown in table 4.

Both the drugs were found to have comparable profiles with regards the parameters studied. There was no significant difference of the total doses of propofol, fentanyl and vecuronium required for the maintenance of anaesthesia in both the groups. The incidence of pain on injection is more in group II patients. The intraoperative haemodynamic e.g. systolic blood pressure and pulse were monitored every 5 min. after induction till the end of surgery. There was no significant difference in both the groups regarding intraoperative haemodynamics as shown in table 6.

Incidence of moderate pain on injection of Propofol emulsion was found to be 62% and in 38% of patients pain was mild .

Figure 1

Table 1: Age Distribution

S. No.	Age Group (yrs)	No. of Patients		Percentage	
		Group I	Group II	Group I	Group II
1.	16-20	2	1	8	4
2.	21-25	4	2	16	8
3.	26-30	3	4	12	16
4.	31-35	14	15	56	60
5.	36-40	2	3	8	12

The table shows the age distribution in both the groups. Majority of patients in both the groups were in the age group of 31-35 years.

Figure 2

Table 2:Sex Distribution

Sex	Group I No. (%)	Group II No. (%)
Male	14 (56)	15 (60)
Female	11 (44)	10 (40)

The table shows the sex distribution with male predominance in both the groups.

Figure 3

Table 3: Haemodynamics

	Group I (Mean ± SD)		Group II (Mean ± SD)	
	Pulse (/min)	Systolic BP (mmHg)	Pulse (/min)	Systolic BP (mmHg)
Baseline	84 ± 3	122 ± 8	82 ± 4	118 ± 4
Just after intubation	90 ± 6	106 ± 5	91 ± 5	104 ± 4
15 min	86 ± 4	103 ± 3	80 ± 4	99 ± 5
30 min	92 ± 3	96 ± 4	76 ± 3	100 ± 3
45 min	82 ± 3	98 ± 3	74 ± 4	95 ± 3
60 min	84 ± 5	95 ± 5	76 ± 4	92 ± 2
120 min	82 ± 3	97 ± 3	78 ± 4	97 ± 3
180 min	79 ± 4	100 ± 2	72 ± 3	103 ± 4
210 min	88 ± 6	100 ± 4	74 ± 4	98 ± 3

($p<0.05$ is significant)

The table shows the stable haemodynamics in the intraoperative period in both the groups.

Figure 4

Table 4: Adverse Reactions

Events	Group I	Group II
Pain on injection	40%	76%
Motor activity	5%	2%
Hypotension	9%	7%
Hypertension	0%	0%
Tachycardia	0%	0%
Bradycardia	2%	3%

The table shows the adverse reactions in both the groups with patients of group II showing significantly greater incidence of pain at the site of injection.

Figure 5

Table 5: Dose Requirement in mg/kg

	Group I (Mean ± SD)	Group II (Mean ± SD)
Induction	2.5 ± 0.23	2.245 ± 0.23

($p < 0.05$ is significant)

The table shows the induction dose which is not significantly different in the two groups.

Figure 6

Table 6

	Group I (Mean ± SD)	Group II (Mean ± SD)
Induction Time (in sec)	68.14 ± 1.26	72.21 ± 1.21
Time of eye opening (in min)	9.68 ± 1.38	10.48 ± 1.36
Time at which patient gets oriented (in min)	19.1 ± 1.91	18.6 ± 2.91
Time at which patient can sit independently (in min)	32.3 ± 2.31	30.1 ± 2.32

($P < 0.05$ is significant)

The table shows that the induction time, the time of eye opening, time at which patient gets oriented, and time at which patient can sit independently are not significantly different in the two groups.

Figure 7

Table 7: Quality of Induction

	Group I	Group II
Grade I	86%	88%
Grade II	14%	12%
Grade III	0%	0%

($P < 0.05$ is significant)

The table shows that maximum patients in both the groups had Grade I quality of induction.

DISCUSSION

The metabolism of propofol is rapid and extensive. Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulphate to produce water soluble compounds. The primary difference between propofol and other sedatives is its rapid onset, extensive distribution and faster metabolic elimination. The recovery profile of propofol is rapid and clear headed with minimal psychomotor impairment and is attributed to rapid redistribution of propofol from the brain.[5,6]

However, emulsion of propofol has a number of disadvantages:

- requires storage at room temperature.
- high risk of bacterial contamination when drawn repeatedly from the vial.
- risk of lipid overload.
- increased risk of post-operative infections.
- pain on injection.

All these drawbacks prompted the search for a safer alternative.

Clear solutions of propofol has a number of advantages –

- It is a clear formulation.
- Has better stability
- Is re-usable, can be drawn repeatedly from the vial
- No risk of bacterial contamination
- Lesser adverse reactions
- No risk of lipid overload.

With Propofol emulsion (group I) the average induction time was 68.14±1.26 sec, the average dose was 2.5±0.23 mg/kg. 86% patients had Grade I and 14% had grade II quality of induction. This is comparable to the study of Cummings et al 1984.[5] They had concluded that induction time (68.8 sec in their study) depends on both the rate of injection and size of the dose. The induction dose in our study was given over 20 seconds.

In group II the average induction time was 72.21±1.21sec, the average dose of induction was 2.245±0.23mg/kg. 88% pts had Grade I and 12% had grade II induction. This is comparable to the results found in the study of Dr. Dasgupta (average induction time 65.7 sec).[11,12]

During recovery, the average time of eye opening in group I was 9.68 ± 1.38min and that of group II was 10.48± 1.36min in our study as shown in table 4.In previous study, the

average time of eye opening in group I was 10 min and in group II was 11min.

Average time at which patients get oriented was as follows- Group I-19.1± 1.91min, Group II- 18.6±2.91sec in our study as shown in table 4. In previous study, this time was 18 min in group I, 20 min in group II.[10] The average time at which patients are able to sit independently was- Group I -32.3± 2.31min, Group II– 30.1±2.32 min in our study as shown in table 4. In previous study, this time was 33 min in group I and 30 min in group II.

Both the drugs were found to have comparable profiles with regards the parameters studied. There was no significant difference of the total doses of propofol, fentanyl and vecuronium required for the maintenance of anaesthesia in both the groups.[7,8] The incidence of pain on injection is more in group II patients.[9] The intraoperative haemodynamic e.g. systolic blood pressure and pulse were monitored every 5 min. after induction till the end of surgery. There was no significant difference in both the groups regarding intraoperative haemodynamics as shown in table

Mild pain on injection of Propofol emulsion was found in 70% patients in the study of P. Picard & Tramer.[9] In our study the results were similar in this group.

76% patients experienced mild pain with clear solution of Propofol. In our study, 62% patients had moderate pain, 38% mild pain.

CONCLUSION

Conclusively, we can state that clear solution of propofol is an equally efficacious alternative to its emulsion preparation. Clear solution can offer many advantages over the emulsion since it is lipid free, easily stored, and can be repeatedly withdrawn from the vial without risk of bacterial contamination. Pain at the injection site was the only drawback we found in the study.

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