INDUCTION OF PROPOFOL WITH COINDUCTION OF PROPOFOL, MIDAZOLAM VERSUS PROPOFOL AUTO COINDUCTION- A COMPARATIVE STUDY

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ABSTRACT

BACKGROUND

Anaesthetic technique used for any surgery in adults comprises of induction with Intravenous (IV) anaesthetic drugs. When used as sole induction agent, drugs like propofol and thiopentone can produce adverse effects on cardiorespiratory system. When induction agent like propofol is combined with a sedative benzodiazepine, midazolam, synergism occurs between these two drugs causing reduction in total dose of primary drug like propofol, a technique called coinduction. Recent studies have shown that if a small dose of propofol itself also called predosing was given prior to induction of propofol, its dose requirement was reduced considerably with less adverse haemodynamic effects. This technique of induction of GA is called auto coinduction.

The aim of the study is to-

1. Find out the total dose of propofol required for IV induction when propofol is used as coinduction agent (auto coinduction) and when a small fixed dose of midazolam is used as coinduction agent (coinduction).
2. Study the effect on haemodynamic parameters and complications in both study groups.

MATERIALS AND METHODS

60 adult patients of either sex belonging to ASA grade I/II and posted for elective surgical procedures under general anaesthesia were randomly divided into two equal groups of 30 patients each. Group A- Auto coinduction group - These patients were given propofol 0.5 mg/kg body weight IV 2 minutes prior to induction with propofol. Group B- Midazolam coinduction group - These patients received midazolam 0.05 mg/kg body weight IV 2 minutes prior to induction with propofol. Total dose of propofol required in both study groups, haemodynamic parameters and complications were studied.

RESULTS

Patients of auto coinduction group required less dose of propofol for induction as compared to patients of midazolam coinduction group. No significant changes in pulse rate in both the groups. Insignificant rise in SBP, DBP and MAP following tracheal intubation in auto coinduction group as compared to that in midazolam coinduction group, which showed highly significant rise in the above parameters. The incidence of side effects in both the groups was low and comparable with no significant difference.

CONCLUSION

Auto coinduction with propofol for induction of anaesthesia is definitely superior to coinduction with midazolam.

KEYWORDS

Propofol, Midazolam, Auto Coinduction, Coinduction.

HOW TO CITE THIS ARTICLE: Aparanji K, Radhasundari M, Gopalakrishna K. Induction of propofol with coinduction of propofol, midazolam versus propofol auto coinduction- A comparative study. J. Evid. Based Med. Healthc. 2017; 4(93), 5670-5674. DOI: 10.18410/jebmh/2017/1138

BACKGROUND

Anaesthetic technique used for any surgery in adults comprises of induction with Intravenous (IV) anaesthetic drugs. The drugs commonly used for this purpose are thiopentone sodium, propofol, ketamine, opioids and benzodiazepine, for example midazolam in doses larger than sedative doses. When used as sole induction agent, drugs like propofol and thiopentone can produce adverse effects on cardiorespiratory system.[1,2] In order to balance the ratio of desired to adverse effects, the concept of coinduction was introduced. The term coinduction has been defined as administration of a small dose of a sedative or other anaesthetic agent to reduce the dose of induction agent. When induction agent like propofol is combined with a sedative benzodiazepine and midazolam, synergism occurs between these two drugs causing reduction in total dose of primary drug like propofol.[3]

Recent studies have shown that if a small dose of propofol itself also called predosing was given prior to induction of propofol, its dose requirement was reduced

Financial or Other, Competing Interest: None.
Submission 18-11-2017, Peer Review 21-11-2017,
Acceptance 06-12-2017, Published 07-12-2017.
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DOI: 10.18410/jebmh/2017/1138

considerably with less adverse haemodynamic effects.[4] This technique of induction of GA is called auto coinduction.

Propofol is a commonly used induction agent and the recommended dose is 2-2.5 mg/kg body weight, when used in this dose, it almost always causes fall in blood pressure, the extent fall in BP depends upon the dose and adjuvants used. Midazolam is a short-acting benzodiazepine and has potent anxiolytic, hypnotic and sedative properties. It also has a fast recovery profile and therefore it is routinely used in preanaesthetic medication.

We have undertaken the present clinical trial in adults posted for various elective surgical procedures to study the effect of midazolam when used as coinduction agent to propofol induction and compare it with predosing of propofol in a small dose prior to propofol induction that is auto coinduction.

MATERIALS AND METHODS

This prospective randomised comparative study was conducted at Department of Anaesthesia, King George Hospital, Visakhapatnam, between April 2016 and April 2017 on sixty adult patients of either sex belonging to American Association of Anaesthesiologists (ASA) grade I/II and posted for elective surgical procedures under General Anaesthesia (GA). Before starting the study, prior permission of the institutional ethics committee was obtained.

All patients were subjected to detailed pre-anaesthetic evaluation and relevant laboratory and other investigations were done. Whenever necessary, other appropriate specialists like physician, cardiologist, etc. were also consulted to improve the medical condition of the patient preoperatively. Written informed consent was obtained from all the patients as per the hospital protocol given at appendix A.

Our Patients' Inclusion Criteria were-

Age 20 to 60 years of both sex, ASA grade I/II posted for elective surgical procedures under GA - General Surgery, Orthopaedic, ENT and Neurosurgery.

Our Patients' Exclusion Criteria were-

Patients not willing to undergo surgery under GA, patients with anticipated difficult tracheal intubation, patients with known sensitivity to drugs under study, pregnant and nursing mothers and patients with any contraindications to use suxamethonium.

All the Patients were Randomly Divided into Two Equal Groups of 30 Patients Each as Follows-

Group A- These patients received propofol 0.5 mg/kg body weight IV followed by remaining dose of propofol (total dose 2 mg/kg) for induction of GA-auto coinduction group.

Group B- These patients received IV midazolam 0.05 mg/kg body weight followed by IV propofol 2 mg/kg for induction of GA.

On the operation table, a suitable vein was secured on left arm and slow IV infusion of ringer lactate was started. The patients were connected to the multiparameter monitor.

Patients were premedicated with glycopyrrolate 0.2 mg and pentazocine 0.3 mg/kg body weight intravenously.

Following preoxygenation with 100% Oxygen (O_2), induction of GA was done in group A with a coinduction dose of 0.5 mg/kg of propofol IV followed two minutes later by induction with propofol till loss of eye lash reflex- auto coinduction.

In group B patients, induction was done with IV midazolam 0.05 mg/kg body weight followed two minutes later by propofol till loss of eye lash reflex.

During induction, pain at the site of injection, respiratory depression and apnoea if any was also noted. Following induction of GA, tracheal intubation was achieved with suxamethonium 100 mg IV and changes in Heart Rate (HR) and blood pressure were recorded at 1 minute and 5 minutes post-intubation.

The surgeon was then allowed to proceed with surgery. Anaesthesia was maintained with Nitrous Oxide (N_2O) 67% in Oxygen (O_2) 33%, isoflurane 0.8 to 1% and vecuronium 0.1 mg/kg body weight and controlled ventilation. During surgery, ringer lactate was infused to replace the fluid loss and colloid/blood was transfused to replace blood loss as and when required. Patient's vital parameters were recorded every 5 minutes.

At the end of surgery, residual effect of vecuronium was reversed with IV glycopyrrolate 0.4 mg and neostigmine 2.5 mg. Oropharyngeal suction was done before tracheal extubation. After ensuring complete recovery, the patients were then shifted to post-anaesthesia recovery room for further management and care.

All the results obtained in both the groups were tabulated and compared clinically as well as statistically. All the data were expressed as means with Standard Deviation (SD). The quantitative data was analysed using test of significance based on t-test. The qualitative parameters were analysed by Chi-square test. Inferences and conclusions of the study were drawn based on the statistical analysis.

OBSERVATIONS AND RESULTS

Parameters	Group A (n=30)		Group B (n=30)		Z Value	P Value
	Mean	SD	Mean	SD		
Age (yrs.)	34.77	7.76	35.03	9.38	0.12	>0.05
Weight (kg)	55.90	8.46	55.73	7.85	0.08	>0.05

Table 1. Comparison of Age and Weight in Study Groups

P value >0.05 - Not significant.

The present study was conducted on 60 adult patients. The age of these patients ranged from 20 to 60 years with the mean age being 34.90 years. The body weight of the patients ranged from 40 to 80 kg with the mean weight being 55.80 kg. There was no statistically significant difference between the two groups with respect to age and body weight (p >0.05).

Dose (mg)	Group A (n=30)		Group B (n=30)		Z Value	P Value
	Mean	SD	Mean	SD		
Calculated	111.80	16.92	111.47	15.69	0.08	>0.05
Induction	61.50	15.93	72.67	13.31	2.95	<0.005

Table 2. Comparison of Calculated Dose and Induction Dose in Study Groups

P>0.05 - Not significant.
P<0.005 - Significant.

The mean total calculated dose of propofol (2 mg/kg body weight) in group A (propofol auto coinduction group) was 111.80 ± 16.92 mg. However, the requirement of induction dose (loss of eye lash reflex) in this group was considerably reduced to 61.50 ± 15.93 mg following coinduction (priming) dose of propofol 2 minutes prior to induction.

In group B patients (midazolam coinduction), the mean total calculated dose of propofol for induction was 111.47 ± 15.69 mg, but the patients required only 72.67 ± 13.31 mg dose of propofol for induction following use of midazolam for coinduction. On clinical as well as statistical comparison between the two groups, it was seen that group A patients require much less dose of propofol (61.50 ± 15.93) as compared to group B patients who needed comparatively higher dose of propofol (72.67 ± 13.31) for induction of GA. This difference in dose requirement of propofol for induction between the two groups was statistically significant (p<0.005).

Pulse Rate (mins.)	Group A (n=30)		Group B (n=30)		Z Value	P Value
	Mean	SD	Mean	SD		
Baseline	83.93	11.24	83.30	12.48	0.21	>0.05
Post priming	79.53	8.96	77	9.81	1.05	>0.05
Post induction	77	8.37	74.90	8.89	0.94	>0.05
Post intubation	84.47	7.92	86.50	9.01	0.93	>0.05
5 mins. after intubation	80.20	7.08	80.40	8.29	0.10	>0.05

Table 3. Comparison of Pulse Rate in Study Groups

P>0.05 - Not significant.

SBP (mmHg)	Group A (n=30)		Group B (n=30)		Z Value	P Value
	Mean	SD	Mean	SD		
Baseline	125.07	10.83	124.03	7.82	0.42	>0.05
Post priming	116.57	9.34	119.70	5.76	1.56	>0.05
Post induction	108.03	10.27	112.37	6.52	1.95	>0.05
Post intubation	119.33	8.15	135	5.59	8.68	<0.0001
5 mins. after intubation	116.93	7.96	126	4.83	5.33	<0.0001

Table 4. Comparison of SBP in Study Groups

P>0.05- Not significant.
P<0.0001- Highly significant.

DBP (mmHg)	Group A (n=30)		Group B (n=30)		Z Value	P Value
	Mean	SD	Mean	SD		
Baseline	78.57	7.46	80.60	7.14	1.08	>0.05
Post priming	73.67	5.88	76.57	6.42	1.82	>0.05
Post induction	67.67	7.359	71.23	6.564	1.98	>0.05
Post intubation	76.10	5.64	86.93	4.91	7.94	<0.0001
5 mins. after intubation	73.17	4.87	79.47	4.17	5.38	<0.0001

Table 5. Comparison of DBP in Study Groups

P>0.05- Not significant.
P<0.0001- Highly significant.

Mean BP (mmHg)	Group A (n=30)		Group B (n=30)		Z Value	P Value
	Mean	SD	Mean	SD		
Baseline	94.10	8.34	94.97	7.09	0.43	>0.05
Post priming	88.03	6.51	90.83	5.81	1.76	>0.05
Post induction	81.17	7.80	85.20	5.97	2.25	<0.05
Post intubation	90.37	5.90	103.10	4.94	9.06	<0.0001
5 mins. after intubation	88.03	5.21	94.87	4.15	5.88	<0.0001

Table 6. Comparison of Mean BP in Study Groups

P>0.05- Not significant.
P<0.0001- Highly significant.

The post induction haemodynamic parameters Pulse Rate (PR); Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure (SBP, DBP, MAP) were studied in both the groups following laryngoscopy and tracheal intubation at 1 minute and 5 minutes. The baseline haemodynamic parameters in both the groups recorded on the operation table prior to administration of preanaesthetic medication were clinically comparable and statistically not significant (p>0.05). The changes in these vital parameters were recorded in both the groups after administration of coinduction dose of the drug under study following main induction dose of propofol and following laryngoscopy intubation. There were no significant changes in PR after coinduction dose of the drug, main induction dose of propofol as well as following laryngoscopy and intubation (p>0.05).

In group A, there was rise in SBP, DBP and MAP at post-intubation as compared to post induction parameters. This rise was however not significant.

In group B, there was statistically significant rise in these vital parameters following intubation as compared with post-induction values.

Complication	Group A (n=30)	Group B (n=30)	Z Value	P Value
Hypotension	3 (10)	0	1.83	>0.05
Fasciculation	9 (30)	6 (20)	0.90	>0.05
Pain	5 (16.67)	3 (10)	0.76	>0.05

Table 7. Complication in Study Groups

P>0.05 - Not significant.

We observed following complications during induction of anaesthesia. In propofol auto coinduction group (group A), 3 out of 30 patients (10%) developed hypotension, while in midazolam coinduction group, no patient developed hypotension. In group A, 9 patients (30%) had fasciculations following suxamethonium administration for tracheal intubation, but only 6 patients (20%) exhibited fasciculations in midazolam propofol group.

Five patients in group A complained of pain on IV injection of propofol, but only 3 patients in group B had pain on IV injection of propofol. However, there was no significant difference in these complications between the two groups (p>0.005).

DISCUSSION

The term coinduction refers to the administration of a small dose of a sedative or other anaesthetic agent to reduce the dose of induction agent.[5,6] The main objectives of this technique are to improve the ratio of desired versus adverse effects and to reduce the cost of expensive drugs such as propofol.[7]

The commonest coinduction agent to propofol has been midazolam.[8,9] Ketamine has also been used as a coinduction agent as it has the advantage of providing cardiovascular stability.[10,11]

Recent studies have shown that if a small dose of propofol itself was given prior to induction of General Anaesthesia (GA) with propofol (auto coinduction), its dose requirement was reduced considerably along with less adverse haemodynamic effects. Therefore, we decided to undertake this study to compare the efficacy of propofol auto coinduction technique with that of midazolam coinduction method for induction of GA. In addition, we also studied and compared haemodynamic response to laryngoscopy and Tracheal Intubation (TI) under anaesthesia using both these techniques.

In our study, we found that both the coinduction agents were effective in reducing the dose of propofol considerably. However, the dose of propofol required for induction was significantly less when propofol was used as coinduction agent (auto coinduction) as compared to induction dose requirement of propofol when midazolam was used as coinduction agent. In this respect, auto coinduction technique using propofol is definitely superior to midazolam coinduction technique. Anil Kumar et al[12] also reported reduction in induction dose of propofol to the extent of 27.48% with auto coinduction technique. Shrivastava et al[13] in their study used midazolam as coinduction agent to propofol induction in a dose of 0.03 mg/kg body weight in one group of patients and observed that induction dose of propofol was less in this group of patients as compared to the patients of other group in whom propofol alone was used for induction. Our findings are also consistent with the observations made by these authors. Many other authors have also reported decreased dose requirement of propofol following preadministration of midazolam[6,8,9] or propofol[7,4] with or without analgesics.

The dose reduction in propofol auto coinduction group was probably due to priming effect.[5] The small subhypnotic dose of propofol prior to its induction dose caused sedation, amnesia and anxiolysis, thus allowing induction of GA with

lower doses of propofol. Predosing and coinduction, both reduce the dose of induction agent required to achieve hypnosis and any form of premedication is likely to have similar effect.[6] The dose reduction following midazolam is probably due to synergistic interaction between the two drugs.[14,3] Synergism has been reported between agents with known functional link in the central nervous system,[14] viz. midazolam and propofol acting on common receptor site, the GABA receptor. Propofol in the recommended dose of 2-2.5 mg/kg body weight almost always causes fall in BP.

The extent of fall in systemic blood pressure depends on dose and adjuvant drugs used. In the present study, there was only minimal fall in SBP, DBP, MAP at different time intervals in both the groups till post induction period, which was not significant (P>0.05). However, in propofol auto coinduction group, there was no significant rise in these vital parameters following TI, but in midazolam coinduction group, there was highly significant rise in SBP, DBP and MAP following intubation (P<0.0001). Thus, it can be concluded that propofol auto coinduction attenuates pressor response to intubation. Coinduction with midazolam does not seem to have this benefit.

The Pulse Rate (PR) changes were also recorded in our study in both the groups at different time intervals till 5 minutes after intubation, which did not show any significant changes (P>0.05). The pulse rate was more or less steady during induction-intubation period. This observation is contrary to the observations reported by other workers[15] who observed significant increase in PR at post induction as well as post intubation in midazolam coinduction group as compared to the baseline values and post-induction/post-intubation values in propofol alone group. They also observed decrease in MAP at post induction. Our observations are similar to the observations made by these authors. However, they observed that post intubation MAP was significantly higher in propofol group than in midazolam coinduction group, but they did not use coinduction technique in propofol group. As the total dose requirement of propofol by coinduction technique in our study was less than the calculated dose on body weight basis, we can assume that cost of this technique for induction of anaesthesia is less than that of conventional method though we have not studied this aspect in details.

The side effects or complications observed in both the groups in our study were of minor nature and transient. The overall incidence of these complications was very low and insignificant with both the techniques and these can be easily prevented.

CONCLUSION

Both midazolam and propofol used in small doses as coinduction agents reduce the requirement of induction dose of propofol for GA considerably, propofol more than midazolam. Technique of propofol auto coinduction is associated with minimal haemodynamic response to tracheal intubation as compared to that with midazolam coinduction. Use of both the drugs is associated with minimum side effects, which are of trivial nature requiring no active treatment. Auto coinduction with propofol for induction of anaesthesia is definitely superior to coinduction with midazolam.

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