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An Observational Study of Small Dose Propofol and Midazolam as Co-induction Agents to Propofol

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Abstract

Introduction: Propofol has become the most widely used I.V. hypnotic agent. It provides rapid induction but the major disadvantages are cardiovascular and respiratory dysfunction hence, the concept of "Auto-co-induction" and "Co-induction" has come forward. The current study, has been designed to evaluate reduction in induction doses of propofol and alteration in peri-intubation hemodynamic in propofol auto-co-induction and midazolam propofol co-induction groups along with propofol group. *Materials and Methods:* The present study, is a prospective, observational and non-interventional study, which includes 75 patients of age between 20 and 50 years with ASA grade I. All the patients were divided into three groups and each group have 25 patients Group I (PP), Group II (MP), Group III (P). Two minutes prior to induction agent Group I received 0.5 mg/kg propofol, Group II received 0.05 mg/kg midazolam. Induction dose of propofol and hemodynamic parameters during various interval were measured. *Results:* Propofol induction dose in Group I,II,III, was 74.4 mg, 66.36 mg and 136.4 mg respectively which was statically significant ($p < 0.05$) when group Iand II compare with group III. Hemodynamic stability in peri-intubation period was better in group I that mean auto-co-induction. *Conclusion:* We conclude that midazolam co-induction and propofol auto-co-induction significantly reduce the induction dose of propofol, propofol auto-co-induction provides better hemodynamic stability in peri-intubation period. The priming appears to be cost effective by significantly reducing the total dose of propofol required and no significant adverse intra-operative or post-operative effects were observed in all groups.

Keywords: Auto-co-induction; Co-induction; Midazolam; Propofol.

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Introduction

An important landmark in the development of anesthesia has been the discovery of an intravenous induction agents. Propofol was introduced in the 1970s and it has become the most widely used I.V. hypnotic agent. It provides rapid induction but the major disadvantages are cardiovascular and respiratory dysfunction hence, the concept of "Auto-co-induction" and "Co-induction" has come forward.

"Auto-co-induction"[1,2] is a technique of giving a pre-calculated dose of induction agent prior to giving the full dose of same induction agent;

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this technique is also known as "the priming technique".[3]

"Co-induction"[4,5] is defined as the concurrent administration of two or more drugs that facilitate induction of anesthesia documenting *synergies*[6] and to decrease the dose requirement of the induction agent to make the quality of anesthesia better with improvement in hemodynamic stability. The commonest co-induction agent to propofol has been midazolam.[7,8]

The current study, has been designed to evaluate reduction in induction doses of propofol and alteration in peri-intubation hemodynamic in propofol auto-co-induction and midazolam propofol co-induction groups along with propofol group.

Materials and Methods

The present study, was a prospective, observational and non-interventional study, which included 75 patients of age between *20* and *50 years* with ASA grade I, posted for various elective surgeries under general anesthesia to Choithram Hospital and Research Center from *March 2015* to *November 2015*.

Approval from the Ethics Committee and Scientific Review Committee and a written informed consent for participation in the study was taken. Pre-operative clinical assessment of the patients was done and on the day of surgery patients were pre-medicated with pre-anesthetic agents. All the patients were divided into three groups in a consecutive manner; accordingly each group has 25 patients:

Group I (n = 25): had received propofol *0.5 mg/kg* + propofol as induction agent.

Group II (n = 25): had received midazolam *0.05 mg/kg* + propofol as induction agent.

Group III (n = 25): had received propofol alone as induction agent.

Baseline measurement of blood pressure, pulse rate and arterial O_2 saturation were taken before placement of IV cannula. Patients were pre-oxygenated with 100% oxygen (*8 L/min*) using face mask and Bains circuit for three minutes, and then were administered fentanyl. *1 mcg/kg* followed by co-induction agent which was *0.05 mg/kg* midazolam (Group II) or *0.5 mg/kg* propofol (Group I).

Two minutes after the co-induction agent injection, each patient received propofol at the rate of *30 mg* every *10 seconds*. Eyelash reflex was checked. If there was no response, propofol injection was stopped, and face mask applied firmly. Any complication during this period, *i.e.*, apnea, vomiting, laryngospasm, involuntary movements, coughing, was noted.

The anesthesia continued according to the standard practice of intubation after rocuronium *1 mg/kg*. Anesthesia was maintained on O_2/N_2O (35%, 65%); inhalational agent, *i.e.*, isoflurane and injection rocuronium. No stimuli were applied during the *10-minutes* post-intubation period.

The following parameters were recorded:

1. Induction dose of propofol.
2. Blood pressure [(systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP)] and heart rate (HR) measured at the following intervals and recorded in a customized performa:

- Baseline (before placement of I.V. cannula);
- Immediately after co-induction agent;
- Immediately after induction agent;
- Immediately after intubation;
- Then at *5 minutes* and *10 minutes.*

The comparison between the three was done using one-way ANOVA. The post-hoc tukey test was applied to find out the statistical difference between the groups.

Results

In the present study, total 75 patients aged between *20 and 50 years* were included and as per study design, they were consecutively divided into 3 groups. Mean age and weight were compared among 3 groups. No statistically significant difference was found among three groups as the f - value is 1.39 and p - value is > 0.05 (**Table 1**).

Table 1: Sociodemographic details

	Mean age	Mean weight
Group I	29.92 ± 7.60	59.28 ± 8.61
Group II	31.88 ± 9.04	57.52 ± 7.48
Group III	28.36 ± 5.27	58.80 ± 6.63

Mean propofol induction dose were compared among 3 groups. Statistically significant difference was found among three groups as the f - value

is 185.28 and p - value is < 0.05. As per post-hoc tukey test the p - value for Group I and Group II pair was found to be > 0.05, which is statistically insignificant and for Group III-II and Group III-I pairs p - value was found to be < 0.05 *i.e.*, statistically significant (**Table 2**). Various hemodynamic parameters at different intervals for all the 3 groups were compared (**Table 3**). At baseline heart rate, systolic and diastolic blood pressure values show statistically insignificant difference as p - value was > 0.05 (**Table 3**).

Table 2: Mean propofol induction dose used in the three groups

	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)
Induction dose	74.40 ± 13.49	66.36 ± 10.66	136.40 ± 17.29

After administration of priming dose (post-priming) of propofol and midazolam in group I and II respectively, the mean heart rate shows statistically insignificant results (p - > 0.05). Same results were obtained in post-hoc tukey test for group I and group II (**Table 3**).

We observed similar results as heart rate for post-priming systolic blood pressure for group I and group II *i.e.*, statistically insignificant values in both ANOVA and post-hoc tukey test (p > 0.05) (**Table 3**).

Whereas post-priming diastolic blood pressure for Group I and group II shows statistically significant results (p - value < 0.05). For pair also the post-hoc tukey test was found to be statistically significant (< 0.05) (**Table 3**).

Again the post-induction heart rate and systolic blood pressure showed statistically insignificant difference between the three groups (p > 0.05). Similarly values of diastolic blood pressure in all three groups showed statistically significant results (f = 10.50 and p < 0.05) (**Table 3**).

For post-induction systolic and diastolic blood pressure post-hoc tukey test showed the p - value < 0.05 for group III-I and Group III and II pair. Thus, there was statistically significant difference between pair, but for group I and II pair p - value was found to be > 0.05 (insignificant) (**Table 3**).

The post intubation heart rate values showed similar variations among all three groups as same as post-induction values *i.e.*, statistically insignificant (p > 0.05). Whereas post- intubation systolic and diastolic blood pressure showed p - value < 0.05 means statistically significant (**Table 3**).

In post-hock tukey test for post-intubation systolic blood pressure showed statistically significant difference among all the three pairs of group, whereas for post-intubation diastolic blood pressure p - value was found to be significant for pair group I–II and group III-II but not for pair group I–III. Heart rate after *5 minutes* shows no significant difference between the three groups (p > 0.05), whereas after *10 minutes* it shows significant variation in values (**Table 3**).

In post-hoc tukey test after *5 minutes* heart rate shows no significant difference among all the three pairs, whereas for after *10 minutes* heart rate statistically significant variation was found between group I and III and group II and III. *5 minutes* and *10 minutes* systolic blood pressure shows statistically significant variation (p - value < 0.05) in all the three groups. Post-hock tukey test shows significant value for pair group I and II and group II and III for systolic blood pressure after 5 and 10 minutes (**Table 3**).

Diastolic blood pressure after 5 and 10 minutes shows statistically significant variation (p - value < 0.05) among all the three groups. Post-hock tukey test shows significant value after *5 minutes* diastolic blood pressure for pair group I–II and I–III, whereas after *10 minutes* significant value was found for pair group I–II and II–III (**Table 3**).

Table 3: HR, SBP and DBP values for all the three groups

	HR			SBP			DBP		
Time Point	**I**	**II**	**III**	**I**	**II**	**III**	**I**	**II**	**III**
Baseline	86.84 ± 11.16	86.28 ± 13.32	84.88 ± 12.70	124.00 ± 10.35	123.64 ± 6.78	125.72 ± 10.50	77.72 ± 7.39	80.12 ± 6.83	80.68 ± 6.93
Post– priming	83.20 ± 10.36	80.68 ± 12.00		117.88 ± 8.88	119.80 ± 4.84		73.12 ± 5.55	77.04 ± 6.43	
Post- induction	77.56 ± 9.12	75.44 ± 8.76	74.48 ± 11.17	108.48 ± 8.97	110.32 ± 7.34	98.04 ± 9.44	67.48 ± 5.50	70.72 ± 6.46	62.56 ± 6.96
Post- intubation	87.84 ± 8.38	88.64 ± 8.31	91.36 ± 12.25	118.16 ± 8.08	135.08 ± 8.48	126.80 ± 12.88	74.36 ± 6.33	94.28 ± 5.73	78.84 ± 8.91
After 5 *min*	80.68 ± 8.65	80.44 ± 7.51	84.60 ± 18.55	112.08 ± 9.32	125.24 ± 8.66	108.80 ± 6.73	69.64 ± 6.16	78.88 ± 5.29	75.88 ± 4.36
After 10 *min*	76.60 ± 8.59	75.96 ± 6.86	82.52 ± 9.99	108.40 ± 8.93	115.24 ± 7.85	104.08 ± 6.37	66.64 ± 5.88	75.48 ± 4.91	64.92 ± 4.28

Discussion

Propofol though a wonderful I.V. anesthetic induction agent with many advantages also has some side effects like hypotension, bradycardia, apnea, etc. which are dose dependent, so a reduction in the induction dose would thereby reduce the associated side-effects, the most important being the effect on cardiovascular system leading to hemodynamic instability.

We found that co-induction agents were effective in reducing the induction dose of propofol considerably compared to propofol alone as an induction agent. Dose reduction following midazolam is probably due to synergistic interaction between the two drugs. Synergism has been reported between agents with known functional link in the central nervous system *viz*. midazolam and propofol acting on a common receptor site, the GABA receptors. The dose reduction in the propofol auto-co-induction group was probably due to 'priming effect'. The small dose of propofol prior to induction dose caused sedation and anxiolysis, thus allowing induction of anesthesia with lower doses of propofol.

In our study, we have observed a significant reduction in the induction dose requirement of propofol in group I (45.45%) as compared to group III which was statistically significant. Our results were similar to Kataria *et al*. (2010)[9] and Amatya *et al*. (2014)[10] they found reduction in dose of induction 31.88% and 27.48% respectively. Group II shows significant reduction in induction dose requirement (51.34%) as compare to group III. Our results were similar to Kataria *et al.* (2010)[9] they found reduction in dose of induction 45.37%. Whereas in Djaiani *et al.* (1999)1 significant reduction of the total induction dose of propofol in both group ($p < 0.001$) were observed.

After induction with propofol heart rate decreased in all the three groups which were 10.68% in group I (PP), 12.56% in group II (MP) and 12.25% in group III (P). Result were not statistically significant between group I (PP) – group III (P) and group II (MP) – group III (P). Our results were similar to Anderson *et al.* (1998)[4] and Srivastava *et al*.[5] they have reported fall in heart rate during induction in all three groups.

After intubation heart rate increased in all the three groups and was statistically not significant. Maximum increase in heart rate from baseline seen in group III (P) (7.63%) and least rise in group I (PP) (1.15%). Our results were similar to Katariar *et al*.[9], they have reported rise in heart rate after intubation least in propofol-propofol group, and maximum rise in propofol group.

After induction systolic blood pressure decreased in all three groups which were 12.51%, 10.77% and 22.01% in Group I, Group II and Group III respectively. Results were statistically significant on comparing Group I–III and Group II–III. Our results were similar to Kumar *et al*.[2]

After intubation, systolic blood pressure increased in all three groups. Maximum rise in systolic blood pressure was observed in Group II (9.25%). Results were statistically significant on comparing Group I–III and Group II–III. Our results were similar to Amatya A *et al*.[10] and Kataria *et al.* (2010).[9]

After induction, diastolic blood pressure decreased in all three groups which was 13.17%, 11.73% and 22.45% in Group I (PP), Group II (MP) and Group III (P) respectively. Results were statistically significant on comparing Group I–III and Group II–III. Our results were similar to Amatya A *et al*.[10] and Kumar *et al*.[2]

After intubation, diastolic blood pressure increased in all groups. Maximum rise in diastolic blood pressure from baseline was observed in Group II MP (17.67%). Results were statistically significant on comparing Group II (MP)–III (P) but on comparing Group I–III statistically insignificant results were obtained and our results were similar to Kataria *et al*.[9] they have reported that after intubation, maximum increase in diastolic pressure was observed in group II (MP) propofol.

Conclusion

From above findings we conclude that midazolam co-induction and propofol auto-co-induction significantly reduce the induction dose of propofol. Propofol auto-co-induction provides better hemodynamic stability in peri-intubation period. The priming appears to be cost effective by significantly reducing the total dose of propofol required and no significant adverse intra-operative or post-operative effects were observed in all groups.

Abbreviation

I.V. - Intra vascular

O_2 - Oxygen

N_2O - Nitrous oxide

SBP - Systolic blood pressure

DBP - Diastolic blood pressure

MAP - Mean arterial pressure

HR - Heart rate

PP - Propofol-propofol

MP - Midazolam-propofol

P - Propofol

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