J Nepal Health Res Counc 2014 Jan;12(26):44-8

A Comparison of Midazolam Co-induction with Propofol Priming in Propofol Induced Anesthesia

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ABSTRACT

Background: Combination therapy with two or more different drugs, with the intension of reaching the same therapeutic goal, was heavily criticized for a long time. However, it is accepted today, especially when advantage over monotherapy can be proved. Our study was undertaken to compare whether propofol priming and midazolam predosing would affect total induction dose requirement of Propofol.

Methods: A prospective randomized, double blind control study was conducted where 120 patients (16-65 years) were divided into 3 groups. Group P received 0.4 mg/kg of Propofol, Group M received 0.05 mg/kg of Midazolam and Group N received 3ml of Normal Saline 5 minutes after intravenous pethidine 0.75 mg / kg given for analgesia. We compared the total dose of propofol requirement for induction of anaesthesia in all the 3 groups, taking loss of verbal contact as the end point. Additionally, changes in haemodynamic status like blood pressure and heart rate at various intervals were studied and compared among the groups.

Results: The groups were similar in terms of age, sex, weight and American Society of Anesesthesiologists Physical Status. The dose of Propofol required to induce anesthesia in Midazolam group was 1.58 mg/kg, 1.86mg/kg in Propofol group and 1.96mg/kg in the control group. There were less hemodynamic changes in Midazolam group compared to the other two.

Conclusions: Pre-dosing with Midazolam is more effective than Propofol priming in reducing the dose of Propofol induced anaesthesia associated with minimum hemodynamic alterations.

Keywords: Co Induction, Priming, Propofol.

INTRODUCTION

Use of multiple anesthetic agents to induce anesthesia is not new and they are used to achieve different effects such as sedation, muscle relaxation and pain relief. Propofol has been accepted as an alternative to Thiopentone for intravenous induction and is commonly used as an inducing agent and its action is more rapid, has rapid awakening and orientation to time compared to Thiopentone.[1] Co-induction has been used to describe the practice of administering a small dose of a sedative or other anesthetic agent to reduce the dose of the induction agent required.[2] Midazolam has been shown to reduce the dose of Propofol required to induce anesthesia by up to 50% without affecting the recover profile when used as" Co- Induction".[3-5] The reduction in the induction dose by applying 'priming principle" could be attributed to the anxiolytic effect of Propofol at sub-hypnotic doses.[6]

METHODS

A randomized control double blind study was conducted at the Department of Anesthesiology at Institute of medicine. One hundred and twenty patients admitted for elective surgery under general endotracheal anesthesia

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were the sample population. Routine pre anesthetic check up was done on the patients a day prior to the day of surgery. On arrival to the anesthesia preparation room, IV access was done with 18 G canula with Ringers Lactate solution. The patients were then transferred to the operation theatre and baseline systolic and diastolic Blood pressure. pulse, heart rate and mean arterial pressure (MAP) were measured. Patients were then assigned into the groups namely: M (Midazolam), P (Propofol) and N (Normal Saline), according to the sealed envelope method (which was labelled with numericals) by the anaesthetic team not participating in the study but the researcher and the patient were unaware of their group. Either of the study drugs as priming were administered IV (Group P- Propofol, Group M-Midazolam,Group N- normal saline) according to the randomization by the team, 5 minutes after analgesia with IV pethedine 0.75mg/kg. 30 seconds after the study drug was given,anaesthesia was induced by injection of 1% Propofol at the rate of 30 mg over 10 seconds until loss of verbal contact by the patient. Endotracheal intubation was done after giving Vecuronium 0.12mg/kg IV as per the guidelines at the department and connected to the ventilator. The researcher measured the hemodynamic parameters before induction, after priming, immediately after induction, one minute and five minutes after intubation. Inclusion criteria included ASA physical status I and II, either sex, age group16 - 60 yrs,Patients scheduled for elective surgeries requiring general endotracheal anaesthesia and the Exclusion criteria included ASA physical status >II,Pregnant and lactating mothers, patients allergic to study medication, patients contraindicated to study drug and patients anticipated for difficult intubation. P value<0.05 will be taken as statistically significant. The obtained data was analyzed by using SPSS version 13.5. Chi-square test and t-test and other tests as applicable.

RESULTS

The mean age of the total patients was 35.75 ± 14.1 years ranging from 16 years to 65 years. In the group M, the mean age was 34.20 years, in group N it was 36.88 years and in group P it was 35.62 years. Out of the 120 cases, 71 were females and 49 males. There were 23 female and 17 male patients in group M, 24 female and 16 male patients in group N and 24 female and 16 male patients in group P. The mean weight of the total patients was 54.48 ± 9.853 kg ranging from 30 to 80 kg. In the group M, the mean age was 53.02 kg, in the group N it was 54.28 kg and in the groups P it was 56.15kg. The majority of the patients in all the three groups were ASA 1 however 9 were in ASA 2 in group P,6 in group N and 5 in group M. Out the 120 surgeries conducted maximum were in Gastrointestinal and minimum in Urology (Table 1).

The average requirement of Propofol varied significantly between the groups, being lowest in Group M (1.58mg/kg) and highest in Group N (1.96mg/kg). The minimum required dose was 0.74mg/kg and maximum of 2.67mg/kg in Group M. The minimum required dose was minimum of 1mg/kg and maximum of 3 mg/kg in Group N. The minimum required dose was 0.25mg/kg and maximum of 3.25mg/kg in Group P (Table 2).

The mean baseline systolic blood pressure was minimum in group M (122.8mmHg) and maximum in group N (130.55mmHg). In comparison to the baseline SBP immediately after induction the SBP decreased in all groups but the maximum decrease was seen in group N by 16 mmHg. One minute after induction there was an increase in SBP which was seen to be maximum in group M. However 5 minutes after induction a decrease was seen in all groups with a maximum in group P 13mmHg. There was no statistically significant difference between the three groups in terms of systolic blood pressure at various intervals .The mean baseline diastolic blood pressure was minimum in group M (76.52mmHg) and maximum in group N (82.1mmHg). In comparison to the baseline DBP immediately after induction, it decreased in all groups but the maximum decrease was seen in group N by 13 mmHg.One minute after induction there was an increase in DBP which was seen to be maximum in group P (7mmHg). However 5 minutes after induction a decrease was seen in all groups with a maximum in group N. There was no statistically significant difference between the three groups in terms of systolic and diastolic blood pressure at various intervals.

The baseline Mean arterial pressure (MAP) was maximum in group N (97.55mmHg) and minimum in group M (91.92mmHg). In comparison to the baseline MAP immediately after induction there was a decrease in all groups and after 1 minute an increase in all groups was observed and after 5 minutes there was a decrease. There was no statistically significant difference between the three groups in terms of mean arterial blood pressure at various intervals (Table 3). The baseline heart rate was 90.52 bpm in Group M, 82.8 bpm in Group N and 81.95 bpm in Group P. These values of heart rates were not statistically significant from each other. However immediately after induction an increase was seen in all groups. One minute and 5 minutes after intubation there was decrease in the heart rate in all 3 groups (Table 4).

Table 1. Comparison of type of surgery among study groups.

	Group P	Group M	Group N
EYE	1	0	3
NEURO	1	0	0
GI	24	14	17
ORTHO	3	4	7
GYNAE	4	2	0
URO	1	1	0
ENT	3	14	8
CTVS	2	3	1
PLASTIC	1	2	4
TOTAL	40	40	40

The clinical significant changes in systolic blood pressure from baseline to various intervals were seen maximum in group N and minimum in Group M.The clinical significant changes in Mean arterial pressure (MAP) from baseline to immediately after induction was seen maximum in Group N and minimum in Group M and Group P, where as changes in MAP from baseline to 1 minute and 5 minutes after intubation was seen maximum in Group P and minimum in Group M.Regarding the heart rate changes from baseline to various intervals, maximum changes were seen in Group M and minimum changes in Group N.

Table 2. Total dose of Propofol in mg/kg among study groups.

	Mean	SD	Minimum	Maximum
Group M	1.58	0.54	0.74	2.67
Group N	1.96	0.51	1	3
Group P	1.86	0.53	0.25	3.25
Total	1.69	0.53	0.25	3.25

Table 3. Changes in MAP among study groups at various intervals.

	Group M		Group N		Group P		Total	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MAP at baseline (mm of Hg)	91.92	11.76	97.55	14.81	92.18	12.12	93.88	13.12
p value M vs. N:0.064 , M vs. P:0.926, N vs. P: 0.080								
MAP immediately after induction (mm of Hg)	81.7	17.64	83.5	14.47	81.48	16.85	82.22	16.26
p value M vs. N:0.619 , M vs. P:0.954, N vs. P: 0.566								
MAP 1 minute after intubation (mm of Hg)	98.22	17.20	101.5	25.02	98.6	23.72	99.44	22.11
p value M vs. N:0.497 , M vs. P:0.936, N vs. P: 0.596								
MAP 5 minutes after intubation (mm of Hg)	87.45	15.12	89.78	18.37	86.05	13.59	87.76	15.76
p value M vs. N:0.538 , M vs. P:0.664, N vs. P: 0.306								

Table 4. Changes in heart rate among study groups at various interval.

	Group M		Group N		Group P		Total	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
HR at baseline (bpm)	90.52	18.243	82.8	17.325	81.95	15.132	85.09	17.248
p value: M vs. N:0.056 , M vs. P:0.065, N vs. P: 0.816								
HR immediately after induction (bpm)	97.2	20.505	83.48	15.908	82.42	14.658	87.03	18.532
p value: M vs. N:0.056 , M vs. P:0.061, N vs. P: 0.782								
HR 1 minute after intubation (bpm)	92.4	17.119	82.7	19.161	80.3	16.018	91.47	17.356
p value: M vs. N:0.864 , M vs. P:0.573, N vs. P: 0.724								
HR 5 minutes after intubation (bpm)	85.1	12.659	81.38	15.702	78	13.251	82.16	14.145
p value: M vs. N:0.590 , M vs. P:0.067, N vs. P: 0.102								

DISCUSSION

The technique of co-induction using two or more agents to induce anaesthesia has been studied and synergism has been reported between a number of induction agents and Midazolam.[3] The potential benefits of synergism in clinical practice would mean that anaesthesia could be induced with a smaller combined total of anaesthetic agents with fewer side effects.[3] A commonly used combination for induction, especially in day-case anaesthesia, is Propofol with a short acting opioid such as Fentanyl. This combination aims to capitalize on the primarily hypnotic and analgesic properties of each drug, respectively. The dose of Propofol required to induce anaesthesia depends on several variables – the end point used, the age of the patient the rate of injection [7,8] and the use of premedication.[9]

Application of the priming principle is a well established fact with use of non depolarizing muscle relaxant where in priming shortens the onset of neuromuscular blockage and provides better intubating conditions. A similar priming principle was applied to the induction dose of Propofol earlier by Maroof et al.[10,11] In our study we evaluated whether "Priming Principle" applied for induction dose of Propofol would affect the total induction dose requirements of propofol and thereby reduce the associated haemodynamic changes.

Predosing with Midazolam is a reliable and effective method of reducing Propofol requirement.[10] Our study has shown that predosing with 0.4mg/kg of Propofol is less effective in reducing the induction dose of Propofol as co-induction with 0.05mg/kg of Midazolam when loss of verbal contact is taken as the end-point. There has been a reduction in dose of Propofol required to induce anaesthesia in Midazolam group (1.58mg/kg) than the Propofol group (1.86mg/kg) and the control group (1.96mg/kg). A similar study done by Cressy DM et al The reduction in older patients was significantly greater than the equivalent response in younger groups.[12] It has also shown a dose reduction of propofol to induce anaesthesia in Midazolam group (1.71mg/kg) and the Propofol group (1.87mg/kg) when compared to the control group (2.38mg/kg).[13,14]

The mean induction dose of Propofol was 80.50 ± 21.95mg in group M, 111.71 ± 27.37mg in group N and 105.62 ± 38.149mg in group P. We observed a 27.9% reduction in the induction dose requirement of Propofol in group M which was less than the other two groups. The reduction in the induction dose in our study was more than that observed by Maroof al (21.4%).[11] Another study conducted by Kumar A et al observed that there was 27.48 % reduction in the induction dose requirement of Propofol by applying priming principle which was similar to our study.[15] In his study both the control group and the Propofol priming group received Midazolam (0.05mg/kg) as a pre-medicant and Fentanyl 15 minutes prior to the induction which explains why a significant reduction of induction dose occurred. In our study Pethedine was used as an analgesic which is less potent than Fentanyl and has been found to have a less synergistic action with Propofol . This could be one of the reasons why dose reduction for induction of Propofol was less in the Propofol primed group in comparison to the control group. Pre-treatment with Midazolam is known to reduce the induction dose requirements of Propofol as studied by Cressy et al.[12]

It was also observed that there was more requirement of Propofol in the control group in comparison to the other 2 groups. There was a greater reduction in blood pressure during induction in the control group compared to other groups but it was not statistically significant. The decrease was not clinically significant as well. It is clear why the control group had a slightly greater reduction in blood pressure as higher doses of Propofol were needed in control group, because the control group did not receive any type of sedation at the start of the study unlike the other two groups, so they remained anxious, ultimately requiring higher dose of propofol.

In our study, although all patients who received Midazolam or Propofol prior to inductions were induced with less than 200 mg of Propofol, two patients in the control group required in excess of 200mg of Propofol which could be due to the fact that their weight were more than 70 kgs . This is comparable with the similar incidence in Godsiff"s study.[14] In his study, although additional Propofol was required in only one of the 19 patients (5%) who did not receive Midazolam prior to induction with Propofol. However, a greater number of subjects would be required to demonstrate a statistically significant difference in the incidence of using more than one ampoule in the control group.

In considering this study and others of its type it is notable that end-points are controversial and difficult to assess. We used loss of verbal contact as end point. Other end-points are loss of eyelash reflex and response to placement of a face mask. However, if we had used a different end-point such as laryngeal mask insertion[7] the results may have been different.[14] In this study we have observed that Midazolam reduces Propofol induction dose requirements. However we have been unable to demonstrate any clear significant benefit in terms of improved cardiovascular stability like other studies.[16] The adverse side-effects of Midazolam should be considered carefully before its use in any patient. A simple reduction in the dose requirement of propofol in the absence of clear benefit, for example in haemodynamic stability,

does not justify its use like in our study however other benefits may exist relating to the amnesic properties of midazolam or effects on the quality of induction which were not taken into consideration in the present study.

CONCLUSIONS

The present study showed pre-dosing with Propofol is less effective than Midazolam in reducing the dose of Propofol to induce anaesthesia This study shows that Midazolam if used as a co induction reduces the required dose of Propofol induced anaesthesia by 27%, so we can recommend midazolam as a co-inducting agent. The haemodynamic consequences require to be clarified and further studies is needed to determine which technique provides the most effective anxiolysis prior to induction of anaesthesia.

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