A Randomized Control Trial Comparing Propofol with Midazolam and Fentanyl Combination for Sedation in Gastrointestinal Endoscopies

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ABSTRACT

Introduction: Propofol can be easily titrated and has a rapid recovery profile, thus has revolutionised sedation practices in gastrointestinal (GI) endoscopy. The objective of this study was to compare efficacy and safety of propofol with midazolam and fentanyl combination for GI endoscopy sedation.

Material and methods: Sixty patients scheduled for gastrointestinal endoscopy were recruited for this study. Patients were randomly allocated into either Group P (propofol alone) or Group MF (combination of midazolam and fentanyl). The parameters used to measure the efficacy were, time of onset of sedation, depth of sedation (Ramsays sedation scale), amnesia and early recovery of sedation (Modified Aldrete Score). Safety was evaluated using cardiovascular and respiratory parameters. Adverse events like hypoxia, hypotension, bradycardia were recorded. PSPP software was used for statistical analysis.

Results: It was observed that P group patients were more deeply sedated with a mean RSS of 5.1 compared to 3.07 of the MF group. Full recovery (Aldrete score 10) at ten minutes after the end of the procedure was seen in 73.33% of the patients of the propofol group compared to 50% of the MF group which was insignificant. Propofol group had significant haemodynamic changes (hypotension) as compared to MF group. Respiratory complications were seen in both the groups but they were few and not significant.

Conclusion: We conclude that both the groups are of same merit and safe.

Keywords: Endoscopist satisfaction, conscious sedation, propofol

INTRODUCTION

Endoscopy in patients with gastrointestinal disorders (GI) is of immense benefit for diagnostic and therapeutic measures. Inspite of use of flexible fibreoptic equipments, endoscopy remains an unpleasant experience for most patients. The purpose of sedation in these patients is to relieve anxiety, discomfort or pain, and diminish memory of the event. Upper endoscopy and colonoscopy are successfully performed using moderate (conscious) sedation. The drugs chosen for sedation should provide ease of titration to the desired level of sedation, and also a rapid return to clear headedness on completion of procedure. Benzodiazepines like midazolam has been used extensively for sedation because it is short acting, has no active metabolites and has great amnestic properties. Propofol is known for its rapid induction and rapid recovery and has deep sedative properties. Despite considerable dispute, propofol has gained overall popularity as the sedative agent of choice and has largely replaced the traditional use of benzodiazepines.[1-3] This trial was undertaken by us with an aim to compare the efficacy and safety of propofol as against midazolam and fentanyl combination for sedation in gastrointestinal endoscopies. The parameters used to measure the efficacy was time of onset of sedation, depth of sedation, amnesia and recovery. Safety were evaluated using cardiovascular parameters (heart rate, blood pressure) and respiratory parameters (respiratory rate, oxygen saturation).

MATERIAL AND METHODS

This study was conducted at Jaslok Hospital and Research centre, Mumbai over a six month period, after departmental review board approval. Informed and valid consent were obtained from the patients. A prospective randomised controlled trial on sixty patients undergoing gastrointestinal endoscopies was carried out, to study efficacy and safety of propofol versus midazolam and fentanyl combination for procedural sedation.

A sample size estimate was calculated from mean values of Ramsays sedation scale of MF and P groups using the formula from ausvet.com.au. Taking variance of standard deviation as 1.22 and maintaining 95% confidence limit and 80% power of study, minimum sample size calculated was 10. We included all 60 patients of ASA I-III undergoing elective gastrointestinal (GI) endoscopies lasting up to one hour.

The endoscopic procedures included were oesophagogastro-duodenoscopy (OGDscopy), endoscopic ultrasound (EUS), endoscpic retrograde cholangiopancreatogra-phy (ERCP) and colonoscopy. Patients excluded from the study were children under18 years, pregnant patients, patients with active GI bleeding, mechanically ventilated patients, allergic to egg or soya beans and those with difficult airway.

A thorough pre-anaesthetic evaluation was carried out in all the patients. Patients were randomised using block of 5 method. 60 patients were divided in two groups of 30 each. Group (MF) received midazolam and fentanyl and Group (P) received propofol 1%. Preliminary data collected were age, sex, weight, ASA status, heart rate, respiratory rate, systolic and diastolic blood pressure and oxygen saturation. After confirming consent and starvation status, intravenous access was obtained. Monitoring included pulse oximetry, electrocardiogram

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(ECG), non invasive arterial blood pressure measurement and graphic analysis of respiratory rate. All patients were given supplemental oxygen through nasal cannula at 4litre /minute. Group MF received injection fentanyl 2µg/kg IV, followed by midazolam 0.05mg/kg slow. When the patient demonstrated signs of sedation like dysarthria, nystagmus or ptosis, sedation was stopped. If the patient achieved the required sedation plane while injecting the drug, the total dose was not given. After one minute of injecting the total calculated dose if the patient did not show any signs of sedation then, an additional dose of 0.5mg of midazolam and 50µg of fentanyl were given. For maintenance, group MF received incremental doses of 0.5mg midazolam and 50µg fentanyl every fifteen to twenty minutes. In group P the patients received intravenous injection of propofol 1mg/kg slowly. After 30 seconds of injecting the total calculated dose, if the patient did not show signs of sedation then, additional increments of 10-20 mg were given. Patients were maintained on 10-20 mg bolus top-ups every five to ten minutes. The time interval between the injection of sedative and the start of endoscopy was recorded as the onset time of sedation. During the procedure the patients were maintained at Ramsays sedation scale (RSS) of 3 or 4. In addition oral and oropharyngeal cavities were topically anaesthetised using three puffs of 10 % lignocaine spray (one puff= 10 mg) in upper GI scopy. In colonoscopy, 2% lignocaine jelly was used in the perianal area prior to insertion.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP),oxygen saturation (SpO_2) and respiratory rate (RR) were measured every five minutes till the end of procedure. Episodes of bradycardia HR< 50 min and hypotension (decrease in SBP< 20mmHg from the base line), were recorded as adverse events. Hypotension was considered as moderate when the decrease in SBP was between 20 and 50 mmHg and severe when it was > 50 mmHg from baseline. Respiratory depression (SpO2 <95 %), airway obstruction and apnoea (no respiratory activity > 15 seconds) were also noted as adverse respiratory events. These were corrected before proceeding further with endoscopy. At the end of the procedure after the scope was removed, the level of sedation was recorded by using the Ramsays Sedation scale. The interval between the removal of the scope till the patients opened their eyes was recorded as awakening time. The modified aldrete scoring system was used to assess the recovery of patients every five minutes thereafter for half hour. Score of 10 was the best score. Patients were assessed for amnesia of intra operative events by subjective questionnaire. Patients were assessed for nausea vomiting and post procedural pain. The endoscopists were given the visual analogue scale to rate the overall satisfaction with sedation and technical ease.

STATISTICAL ANALYSIS

Qualitative data that included gender, weight, ASA grade was assessed by Chi square test and by Fisher's Exact test. Quantitative data was represented by using mean ± SD and analyses between the groups were done by using unpaired t-test and Chi square test. Statistical software, PSPP was used for statistical analysis.

RESULTS

Sixty patients were studied in our trial. The demographic data is summarised in Table-1. Patients in the MF group received mean dose of 2.48mg and 129 µg of midazolam and fentanyl for induction and Group P achieved sedation with the mean induction dose of 63.3 mg. Group P had mean onset time of action of 44 seconds compared to MF group, in which it was 85.33 seconds which was statistically significant. Total mean dose for maintenance required in Group MF was fentanyl 173µg and midazolam 3.25 mg. In group P total mean maintenance dose was 180.83 mg (6 mg/kg/hr). It was observed that at the end of procedure patients in the P group were more deeply sedated with a mean RSS of 5.1 compared to 3.07 of the MF group. This difference was statistically significant. The time to awaken the patients in the P group was significantly more, which was 2.47 min compared to 0.07 min in the MF group. Recovery was assessed using the Modified Aldrete System at the end of the procedure. At 10 min after the end of the procedure 73.33% of the patients in the propofol group were fully recovered with a score of 10 compared to 50% of the MF group which was statistically insignificant (P 0.11). At the end of 30 minutes all the patients in both the groups had recovered except one patient in the P group and two patients in the MF group. Recovery time of both groups was almost same (11.5 +/-8 min in the MF group vs 10.3 +/- 5 min in the P group) which was not significant (Table-2).

We observed 46.6% of patients in the P group had hypotension which was statistically significant. 4 patients had severe hypotension and 10 patients had moderate hypotension. In the midazolam group only three patients had moderate hypotension. No patients had bradycardia <50 /min or ECG changes. Mean fall in systolic blood pressure in the MF group was 14.54 mmHg which is clinically not significant. Mean decrease in the SBP in the P group was 33.27mmHg which was significant clinically. Mean percentage decrease in the in SBP from the baseline was significantly more in the P group. It was 11.3% in the MF group compared to 23.26% in the P group. There was no significant difference in the mean percentage decrease in the diastolic blood pressures as well as heart rate between the groups. The incidence of airway obstruction was more in group P. Respiratory depression was seen in five patients in group MF compared to two in the P group. Two patients in both groups had apnea transiently. In the MF group the mean lowest saturation and respiratory rate were less from the baseline. This was statistically significant. In the P group also there is significant difference between baseline respiratory rate and its mean lowest.

	MF (Mean± SD)	P (Mean)	P value
Age (Yrs)	50.93 ± 16.68	52.7± 17.06	0.687
Weight (kg)	61.27± 9.9	63.37±13.36	0.492
Duration of procedure (min)	23.67± 12.52	20.17± 13.68	0.305
* P < 0.05 significant, MF - Midazolam Fentanyl, P- Propofol			

Table-1: Demographic characteristics. The results are given as mean or median (SD).

No such difference is seen with saturation in the P group. The mean percentage decreases in saturation were equivalent in both the groups and insignificant. The mean decrease in the respiratory rate (RR) in the MF group was significantly more compared to the P group (20% versus 10.9%) (Table-3).

Endoscopists satisfaction was graded using the visual analogue scale (VAS). Mean VAS in the MF group was 80.67% compared to 77.5% in the P group (Table-2). The difference was insignificant. Patient tolerance was assessed by a subjective questionnaire in terms of amnesia, post operative pain, nausea and vomiting. 43% of patients in the MF group could recall the procedure done, either partially or completely compared to 6.7% of the patients in the P group. This was statistically significant (P 0.001). Thus 93.3 % of patients of P group had amnesia. Only one patient of MF group had pain post procedure and two patients of the P group had nausea and one vomited. During scope insertion, some patients showed resistance in the form of coughing, gagging and hiccups in both groups, however the difference is insignificant

DISCUSSION

Anaesthetic management in gastro intestinal endoscopies is confined to either topical anaesthesia or its combination with sedation. Propofol is a short-acting anaesthetic agent that has a favourable pharmacokinetic profile in comparison to the benzodiazepines and opioids with regard to rapid induction of sedation, faster recovery, and equivalent levels of amnesia. Midazolam is a benzodiazepine depressant of the central nervous system that is commonly used in synergy with opioid fentanyl for conscious sedation during GI endoscopy. This combination has some limitations like a delay of onset of action, lingering sedative effects that delay discharge, and prolonged recovery, and morbidity as a result of respiratory depression. Therefore optimal propofol administration methods for gastrointestinal procedures needs to be studied further.

Propofol follows a rapid redistribution pattern after injection, hence top up interval for the propofol group was more frequent in our study than the MF group. As a result to maintain the level of sedation and prevent the patient from waking up during the procedure, closed titration of propofol was required. In a study done by Christopher N, quality of sedation, operating conditions, and recovery profiles were similar in intermittent bolus injections, conventional syringe infusion and target controlled infusion.[4] Sedation level was assessed at scope removal. It was not assessed during the procedure so as to prevent and minimise interruptions. In MF group synergistic effect of the two drugs helped in maintaining the patients at a moderate level of sedation. In our study the propofol group patients were deeply sedated. Propofol does not have analgesic properties, it has a narrow therapeutic window and absence of a reversal agent can lead to over sedation.[5] Deep sedation can increase the cardiovascular complications like hypotension and bradycardia and also depresses airway reflexes resulting in gastric aspiration. Airway patency can also be compromised and ventilation may need to be assisted. In our study patients receiving propofol were more deeply sedated, however there was no incidence of aspiration. Therefore to reduce complications balanced propofol sedation was proposed as a method that would provide safe and effective sedation by combining a low dose of propofol with opioid analgesic and or benzodiazepine.[6,7]

Amnesia for the total procedure is important because it improves patient tolerance and acceptance for any repeat endoscopy. More number of patients in the propofol group (93.3%) had amnesia as compared to MF group (56.7%) which was significant (P =0.001). This could be because of deeper plane of sedation in the P group. Our study is contrary to the study of K.W Patterson et al.who showed that 68 % of midazolam group were amensic compared to 14 % of the propofol group.[8] In his study only single bolus technique was used with both drugs. The induction dose of midazolam was much higher (0.08mg/kg) compared to our study.

In the combination group, last top up of drug was given 10 to15 min prior to the completion of the procedure. However in the propofol group last top up was given few minutes prior. It was thus observed that more number of patients had full recovery immediately after awakening in the combination group as compared to propofol group. At the end of 30 minutes most of the patients in both groups had completely recovered. On an average recovery time in both groups was almost same with majority of patients in the propofol group recovering in the first 10 minutes.

This could be due to the rapid clearance and rapid redistribution of propofol. In 2002 Sipe et al compared the use of propofol versus midazolam plus meperidine in 80 patients undergoing

	MF (Mean ± SD)	P (Mean ± SD)	P value
Onset of sedation (s)	85.33 ± 41.89	44 ± 24.37	<0.001*
Ramsays Sedation Scale	3.07 ±1.05	5.1± 1.49	<0.001*
Awakening (Min)	0.07±0.22	2.47± 2.28	<0.001*
Recovery Time (min)	11.5± 8	10.3± 5	0.48
Endoscopist Satisfaction (VAS %)	80.67±10.73	77.5± 11.95	0.28
* P<0.05 is significant MF- Midazolam Fentanyl, P - Propofol, VAS - Visual analogue scale			

Table-2: Comparison of efficacy between the two groups. The results are given as mean or median (SD).

	MF (Mean)	MF (SD)	P (Mean)	P (SD)	P value
SBP % decease over baseline	11.03	8.52	23.26	13.06	<0.001*
HR % decrease over baseline	7.65	8.45	6.37	6.42	0.51
RR % decrease over baseline	20.03	18.47	10.95	15.45	0.043*
Saturation % decrease over baseline	1.37	3.22	1.83	5.62	0.69
*P<0.05 is significant, MF- Midazolam Fentanyl, P- Propofol; SBP - Systolic blood pressure, HR- Heart rate, RR- Respiratory rate					

Table-3: Comparison of safety parameters. The results are given as mean or median (SD).

colonoscopy. Mean time to sedation was significantly faster with propofol, the depth of sedation was greater and also these patients recovered faster.[9] By 30 minutes all patient had achieved full recovery in the propofol group compared to 65% in the midazolam group. Mean dose of midazolam was 4.7 mg with mean duration of 12.2 min compared to our study where the mean total dose was 3.25mg with mean total duration of 23.6 minutes. Therefore in our study recovery of patients in the MF group at the end of 30 min is much higher (93.3%).

T.W. Weherman et al[10] studied patients for ERCP who received either midazolam pentazocine combination or propofol for sedation. Full recovery was achieved after 19 +/- 8 min in the propofol group compared to 29+/- 8 min in the midazolam group. This is contrary to our study in which the mean recovery time was much shorter in both the groups (10.3+/- 5 min in P vs 11.5 +/- 8 in the MF group). This could be because the total doses of propofol (388+/- 212 mg) and midazolam (7.8+/- 3.1 mg) used were much higher compared to our study.

Vargo et al[11] did a similar study in 2002 in 75 patients undergoing advanced upper GIscopy. He compared sedation between propofol and midazolam meperidine groups. Recovery time was much shorter in propofol group (18.6 min vs 70.5 min). At the end of 15 min 76 % in propofol group achieved full recovery compared to 8% in the midazolam meperidine group. In our study also at 10 min 73.3% of patients in the Propofol group had full recovery compared to 50 % in the MF group. Fentanyl is shorter acting drug than pethidine. Total dose of midazolam used in Vargo study (9.2mg) was much higher. Hence the recovery of patients in the midazolam group was much more delayed compared to our study.

In our study all patients received 4 liters/ min of oxygen throughout the procedure. It was observed that during the procedure, two patients in each group were apnoeic transiently, immediately following bolus injections. These patients started breathing immediately after gentle tapping or calling out their names. Respiratory depression was observed more in the MF group. Five patients in the propofol group and two in the MF group experienced airway obstruction. Clinically no patient had respiratory rate less than 10 per minute. The mechanism of respiratory depression in the midazolam fentanyl group was due to the significant blunting of the hypoxic ventilatory drive resulting in hypoventilation and decrease in the respiratory rate. In T.W. Weherman study mean percentage decline in the oxygen desaturation was greater in the propofol group (5% +/-3%) than the midazolam group (3% +/- 2%).[10] A drop in saturation less than 90% was seen in 11/98 patients in P group compared to 8 in the midazolam group. In our study, the mean percentage decrease in saturation (P 1.83 +/- 5.62% vs MF 1. 37 +/- 3.22) was equivalent in both the groups and insignificant.

Vargo et al observed a decrease in in mean arterial blood pressure in both the groups with no significant difference.[11] Hypotension was seen in 6/38 in P group and 3/37 in the M group. In 2004 Ian et al did a prospective study in 500 patients for upper GI endoultrasonography.[12] Propofol was given as bolus 25-45 mg followed by infusion 25mcg/kg/min. There was no hypotension, tachycardia or bradycardia. He studied only young and healthy ASA 1 and 2 patients. In our study propofol was given as bolus top ups and maintained a 100 mcg/kg/ min and hence the hypotension.

In our study we found that 14 patients of the propofol group had hypotension compared to three in the MF group, which was statistically significant. Four patients in the P group had severe hypotension which needed treatment. There has been a statistical significant decrease in the arterial pressures (systolic and diastolic) from their baselines in both the groups. However mean decrease in the SBP in the MF group was 14.54 mmHg which was clinically insignificant as compared P group in which the mean decrease was 33.27 mmHg. Statistically it was seen that the mean percentage decline in SBP in the P group was significantly more than the MF group (23.26%in the P group compared to 11.03% in the MF group). There was statistical decrease in heart rate from the baseline in both groups, but it was not clinically relevant.There was no incidence of bradycardia or arrhythmias. It is known that a induction dose of propofol causes 20-30 % decrease in blood pressure. Midazolam and fentanyl both decrease the systemic vascular resistance and can cause decrease in blood pressure. But they do not depress the myocardium as compared to propofol. We have included in our study ASA 3 patients. These patients may not be able to compensate for the vasodilatory actions of propofol. Thus clinically in an endoscopy suite propofol can cause unacceptable hypotension in ASA 3-4 patients.

23% of the patients in the P group complained of pain on injection of the drug propofol. All patients in both the groups except one in the MF group were pain free postoperatively. Pain in the postoperative period could be due to abdominal distension, especially in prolonged cases or some therapeutic procedure like sphincterotomy. Post operative nausea vomiting is an important frequent complication in GI endoscopies. Only two patients had nausea in the P group and one of them vomited. Propofol has an antiemetic property and fentanyl even though being an opioid has the least emetogenic effect.

The endoscopists were very satisfied with sedation in both groups (80.67% MF vs 75.57% in P group) the difference was insignificant. The endoscopists were not blinded in our study which could be responsible for greater and similar satisfaction score. These finding were similar to the study done by Eszter Sego et al.[13]

Limitations of study

In our study amnesia was assessed only by subjective questionnaire. Sophisticated techniques like the visual memory test were not used. We have not included in this study home readiness and other psychomotor tests which assess discharge criteria.

CONCLUSION

We conclude that both the groups are of merit and safe. Quality of sedation is more ideal with propofol, with deeper sedation than required. An additional feature of propofol is its early recovery. Haemodynamic variations (more with propofol) and respiratory complications are seen with both groups. Theses can marginalised completely with eternal vigilance and timely correction

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