

POST OPERATIVE NAUSEA AND VOMITING IN AMBULATORY SURGERY: COMPARISON OF MIDAZOLAM WITH NORMAL SALINE

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ABSTRACT

Objectives: To compare the efficacy of intra-venous midazolam for prevention of post-operative nausea and vomiting in comparison with normal saline (placebo) in ambulatory endoscopic procedures.

Material and Methods: This study was conducted at Department of Anesthesiology at Institute of Kidneys Diseases and Critical Care Hayatabad Medical Complex Peshawar on 70 patients of either sex, 35 in each group. Group A(n-35) received midazolam and Group B(n-35) Normal saline (placebo) prior to induction of general anesthesia. Only those patients were included who fulfilled our inclusion criteria and assessed for episodes of post-operative Nausea and vomiting at 1 to 6 hours postoperatively. Study design was randomized controlled trial.

Results: During 1st post operative hour up to 66% patients in group "A" had complained for nausea and vomiting in which 40% patients had complained for nausea and 26% patients complained for vomiting. While 71% patients in group "B" had complained for nausea and vomiting in which 28% patients had complained for nausea and 43% patients complained for vomiting. Similarly after 6th hour 22% patients in group "A" had complained for nausea and vomiting in which 14% patients had complained for nausea and 8% patients complained for vomiting. While 48% in group "B" had complained for nausea and vomiting in which 20% patients had complained for nausea and 28% patients complained for vomiting.

Conclusion: We concluded that midazolam 50-75µg/kg i/v preoperatively significantly decreases the incidence of nausea and vomiting in Patient undergoing ambulatory (day care) endoscopic procedures under general anesthesia.

Key Words: Nausea, PONV, Risk factors, vomiting.

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INTRODUCTION

Postoperative Nausea and Vomiting (PONV) is one of the most unpleasant and stressful act during practice of general anesthesia and surgical procedures¹, frequently hampering practice of ambulatory (day care) surgery², a most frequent and common problem with no single mod solution³. Despite significant researches in the field of PONV and the introduction of new and different classes of anti emetic agents the

overall incidence of PONV is currently estimated to be around 20-30%⁴ in patients undergoing even minor day care endoscopic surgical procedures. The risk of PONV is much high with risk factors for PONV i,e 75%^{5,6}. The risk factors are anxiety, pain, anesthetics, type of surgery(endoscopic) and duration of surgery etc.

PONV mostly affect patient satisfaction and well being leading to prolong stay in recovery room and may lead to unnecessary admission to the hospital leading to increase cost. Each vomiting act hampering discharge criteria of the recovery room nearly with delay of 20 min⁷. PONV causes 0.17% unnecessary admissions to the indoor hospital following day care surgeries due to hypovolemia (dehydration), electrolytes disturbances, wound disruptions (dehiscence), esophageal injuries like rupture⁸ and serious airway compromise like burns and aspiration lung injuries pneumonitis, although the more severe complications are rare.⁹

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Controversy continues in the management of PONV despite the newly and effective availability of anti emetics such as 5-HT₃ receptor antagonist like ondansetron, tropisetron, granisetron and ramosetron which are too much costly, while anti-histaminic, anti-cholinergic and dopamine antagonist are at the cost of unfavorable side effects like extra pyramidal side effects, mouth dryness¹⁰, hypotension and unwanted side effects like irritability, restlessness and hallucinations.

In several studies, benzodiazepines group of drugs have been shown to improve wellbeing and decrease anxiety. Anxiety is too considered a risk factor for PONV. Benzodiazepine like lorazepam has been reported to be reducing the severity of PONV¹¹. However, its slow mode of onset of action and prolonged duration can result in undesirable sedation that last longer. Midazolam is a short-acting benzodiazepine having rapid onset of action, which is used for co-induction in general anesthesia and preoperative anxiety. Recently midazolam has been used frequently for prophylaxis of PONV peri-operatively either in bolus or postoperative continuous infusion¹²⁻¹⁷. The pre operative intravenous midazolam 50-75 µg/kg decreases the incidence and acuteness of PONV after general anesthesia for patients undergoing cholecystectomy¹⁸. More recently patients with refractory PONV not responding to others antiemetic have successfully treated with midazolam infusion in small dosages in comparison with Placebo.

The midazolam mechanism of action is not known exactly. Postulated mechanisms of actions include potentiates inhibitory effects of glycine, potentiates inhibitory effects of inhibitory neurotransmitter gamma amino butyric acid (GABA), potentiates adenosine effects and enhance inhibition of dopamine. Benzodiazepines have been proposed to enhance inhibition of dopamine in the chemoreceptor trigger zone through release of adenosine producing antiemetic effect. A very precise mechanism of action of midazolam needs to be determined but our clinical experience is with current postulations of anti-dopaminergic activity based antiemetic. Antiemetic dose-response curves for midazolam are not currently available. It is unknown whether smaller doses are as effective and whether larger doses would be more effective. Thus we conclude that midazolam 50-75µg/kg as an effective prophylactic antiemetic in addition to decreasing anxiety¹⁹.

Aim and objective of this study was to evaluate the antiemetic effect of midazolam and normal saline (placebo) in ambulatory (day-care) endoscopic surgeries where the incidence of postoperative nausea and vomiting is high, based on the results of this study.

MATERIAL AND METHODS

This study (randomized controlled trial) was conducted at Department of Anesthesiology Institute of Kidney Diseases and Critical Care, Hayatabad Medical Complex (HMC), Peshawar from April 2013 to April 2014 after approval from Hospital Ethical Committee, Total 70 patients of either sex of ASA grade 1 and 11 were divided, into, two; groups, Midazolam Group A (n=35) and Placebo Group B (n=35). All patients of age range 20-40 years with physical status ASA grade 1 and 11 undergoing Ambulatory (day care) endoscopic procedures were included in the study. All those patients with history of Travelers (motion) sickness, vestibular apparatus disease, patient received anti emetic therapy within 24 hours, patients develop intra-operative hypotension were excluded because of increased incidence of nausea and vomiting, acted as confounders. It was also planned that if there is occurrence of PONV in both groups, rescue anti emetic will be given.

Informed written consent for general anesthesia was obtained from all patients. Since each patient's allocation was determined in advance by their sequence of presentation, 70 envelopes 35 for each group were made and a randomly-selected envelope was opened when the patient presented. Only those patients were included who fulfilled our inclusion Criteria i.e. undergoing Ambulatory (day care) procedure.

Anesthetic technique was standardized for all the patients including type of anaesthesia, duration of anaesthesia, duration of surgery and medicines used for induction and recovery in both groups, to control confounding factors. Patients in Group (A) received midazolam 50-75 µg/kg diluted with saline up to 10ml and Group (B) received 10ml of saline (placebo) just before induction of anesthesia. All patients received General anesthesia including iv propofol 2-2.5mg/kg, i/v Tramadol 1-3mg/kg, i/v Acuron 0.5mg/kg and anesthesia was maintained with isofluran, oxygen-nitrous oxide technique. Standardized monitoring applied to all including NIBP, Spo2 and ECG. The duration of surgery limited to 30 to 50 minutes. All patients received ringers lactate solution 30ml/kg/hour After the completion of surgery patients were shifted to recovery room where they were kept for one hour and observed for PONV and sedation, using 3-Point Ordinal Scale (0-none, 1-nausea, 2-vomiting) and sedation score respectively. Postoperative care was standardized. Rescue antiemetic (metoclopramide 10mg i/v) were administered to patients on demand. After one hour patients were shifted to ward and observed for PONV for first 6 hours with the help of trained nurses. The results were evaluated with help of Chi square test and recorded in the Performa.

RESULTS

In this study a total of 70 patients were taken for endoscopic ambulatory surgery in the Institute of Kidney Diseases and Renal Transplant, Hayatabad Medical Complex. All the 70 patients were divided into two groups (35 patients in each group). Midazolam was given to the patients in Group A (n=35) while normal saline was given to the patients in Groups B (n=35).

Age distribution among the two groups was analyzed as in Group A most of the patients 20(57%) were in age range 20-30 years and 15(43%) patients were in age range 31-40 years. Mean age in this group was 31 years with standard deviation ± 5.61 . In Group B 18(52%) of patients were in age range 20-30 years and 17(49%) patients were in age range 31-40 years. Mean age in this group was 30 years with standard deviation ± 4.32 (Table 1).

Weight distribution among the two groups was analyzed as in Group A 7(20%) patients were in weight

range 46-50 Kgs 5(14.29%) patients were in weight range 51-55 Kgs, 7(20%) patients were in weight range 56-60 Kgs, 8(22.85%) patients were in weight range 61-65 Kgs, 4(11.22%) patients were in weight range 66-70 Kgs 4 (11.22%) patients were in weight range 71-75 Kgs. Mean weight in this group was 54 Kgs with standard deviation ± 12.34 . In group B 7(20%) patients were in weight range 46-50 Kgs, 6(17%) patients were in weight range 51-55 Kgs, 4(11%) patients were in weight range 56-60 Kgs, 8(22.85%) patients were in weight range 61-65 Kgs, 2(6%) patients were in weight range 66-70 Kgs, 8(22.85%) patients were in weight range 71-75 Kgs. Mean weight in this group was 56 Kgs with standard deviation ± 11.86 . (Table 2).

Incidence of nausea and vomiting at 1st hour post operatively among the two groups were analyzed as 23(66%) patients in Group A had complained for nausea and vomiting in which 14(40%) patients had nausea and 9(26%) patients had vomiting. While in

Table 1: Age distribution of two groups (n=70)

Age Distribution	Midazolam (n= 35)	Saline (n=35)	Total
20-30 years	20 (57%)	18 (52%)	38
31-40 years	15 (43%)	17 (49%)	32
Total	35	35	70
	Mean age was 31 year SD ± 5.61	Mean age was 30 year SD ± 4.32	

Chi square test was applied in which P value = 0.00

Table 2: Weight distribution of two groups (n=70)

Weight Distribution	Midazolam (n= 35)	Saline (n=35)	Total
46-50 Kgs	7(20%)	7(20%)	14
51-55 Kgs	5(14.29%)	6(17%)	11
56-60 Kgs	7(20%)	4(11%)	11
61-65 Kgs	8(22.85%)	8(22.85%)	16
66-70 Kgs	4(11.43%)	2(6%)	6
71-75 Kgs	4(11.43%)	8(22.85%)	12
Total	35	35	70
	Mean age was 54 Kg SD ± 12.34	Mean age was 56 Kg SD ± 11.86	

Chi square test was applied in which P value = 0.01

Table 3: incidence of nasea and vomiting in two groups

Incidence		Midazolam (n=35)	Saline (n=35)	P-value
In PACU 1st hour post operatively	Nausea	14(40%)	10(28%)	0.01
	Vomiting	9(26%)	15(43%)	
Total		23(66%)	25(71%)	
In ward 6 hours postoperatively	Nausea	5(14%)	7(20%)	0.005
	Vomiting	3(8%)	10(28%)	
Total		8(22%)	17(48%)	

Table 4: Incidence of sedation in two groups (n=70)

Incidence of Sedation		Midazolam (n= 35)	Saline (n=35)	P-value
At 10 minutes	Yes	2(6%)	Nil	0.03
	No	33(94%)	35(100%)	
At 20 minutes	Yes	2(6%)	Nil	
	No	33(94%)	35(100%)	
At 30 minutes	Yes	2(6%)	Nil	0.02
	No	33(94%)	35(100%)	
At 1 hour	Yes	1(3%)	Nil	0.001
	No	34(97)	35(100%)	
At 2 hour	Yes	Nil	Nil	0.000
	No	35(100%)	35(100%)	

Table 5: Metoclopramide (Maxolon 0.1 – 0.2 Mg/kg i.v) (n=70)

Metoclopramide	Midazolam (n= 35)	Saline (n=35)	Total
Given	1(3%)	4(11%)	5
Not Given	34(97%)	31(89%)	65
Total	35	35	70

Chi square test was applied in which P value = 0.04

Group B 25(71%) patients had complained for nausea and vomiting in which 10(28%) patients had nausea and 15(43%) patients had vomiting. Similarly after 6th hour Group A 8(22%) patients had complained for nausea and vomiting in which 5(14%) patients had nausea and 3(8%) patients had vomiting. While in Group B 17(48%) patients had complained for nausea and vomiting in which 7(20%) patients had nausea and 10(28%) patients had vomiting. (Table 3).

Incidence of sedation at 10, 20, 30, 60, 120 minutes among the two groups was analyzed as in Group A sedation was found in two patients 10-30 minutes but after 1 hour only one patient had sedation which was finished up to 2 hours. While in Group B sedation was not found in any of the patients. (Table 4). Status of rescue drugs among the two group was analyzed and in Group A 1(3%) of patients received metoclopramide as a rescue antiemetic to control PONV. In Group-B 4(11%) of patients needed it to combat PONV during the 6 hours follow up period. (Table 5).

DISCUSSION

Endoscopic procedures have decreased surgical morbidity and mortality and have become a popular technique for an ambulatory 20 (day care) setting with least complications, reduced cost of surgeries, reduced stay in hospital and faster recovery. Although Endos-

copy is not a benign procedure traumatic injuries to viscera and vessels may be more common than with open surgery. The reported incidence of PONV after endoscopic day care surgery is as high as 54-92%². It can be reduced by using good antiemetic peri-operatively. In our study we found that the prophylactic use of midazolam significantly reduces the incidence of PONV in patient undergoing endoscopic ambulatory surgical procedures.

The use of Benzodiazepines in the management of PONV has been reported in the literature, both for prophylaxis and treatment. In the pediatric field of anesthesia and surgery, several research studies have demonstrated marked decrease in PONV following tonsil and squint surgeries when midazolam or lorazepam were used for prophylaxis²¹. Midazolam was too helpful in cases of refractory and persistent PONV²² not responding to others antiemetic. Midazolam was also found effective antiemetic in patients receiving anticancer drugs treatment²³.

All endoscopic procedure underwent on ambulatory patients with a standardized anesthetic techniques and surgical procedures. The duration of anesthesia, duration of surgery, type of surgery and the type of anesthetics used were similar in the two groups. Therefore it is likely that the differences in the incidence of PONV between groups are contributed to Midazolam rather than to any confounding variable.

The prophylactic effects of midazolam in preventing PONV following epidural opioids (morphine) for postoperative analgesia has been associated with a high incidence of PONV²³. The use of opioids for analgesia is also a strong risk factor for PONV. Propofol and midazolam used in sub-hypnotic doses were as effective as ondansetron in treating PONV in patients undergoing abdominal or gynecological surgery without untoward sedative or cardiovascular effects¹⁰.

We also observed that midazolam in lower dosages as a premedication or intra-operative bolus administration did not prolong the duration of anaesthesia, increase the degree of sedation and increase the postoperative stay in the recovery room. Midazolam administration preoperatively did not significantly affect peri-operative thermodynamics or vital signs⁸.

In our study incidence of sedation at 10, 20, 30, 60, minutes was observed, as in Group A sedation was found in two patients from 10-30 minutes in which the mean sedation score was 2 but after 1 hour only one patient had sedation which was finished up to 2 hours. As the reported sedation level in number of patients is low because of low dosages of midazolam (50 to 75 µg/kg) we have used in our study While in Group B sedation was not found in any of the patients because of use of normal saline (placebo).

In our study, we reported a significant (P = 0.04) lower use of rescue antiemetic (3%) in the group A when compared with the NS (11%) in group B. So it was found that the incidence of PONV was significantly less as compared with the placebo group. As midazolam is freely available. Economical and the single dose was not associated with any significant side effect, it should there be used more frequently in endoscopic ambulatory procedure (surgery). We further suggest that varying doses of midazolam should be compared with a placebo to evaluate its anti-emetic properties. The incidence of postoperative Nausea and Vomiting (PONV) has been reported to be 46% with the use of benzodiazepines such as midazolam compare to 79% with placebo when used prophylactically in patients undergoing cardiac surgery¹⁶.

CONCLUSION

The midazolam 50-75µgm/kg significantly decreases the incidence of nausea and vomiting in patients undergoing ambulatory endoscopic procedures with least requirement of rescue anti-emetics and it is much effective than placebo and contributed to a decreased incidence of unscheduled admissions to hospital.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Qadirullah: Idea of concepts, manuscript of writing, data collection and Review of literature.

Tariq MA: Review of literature and manuscript proof reading.

Iqbal Z: Help data collection

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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