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ORIGINAL ARTICLE

Comparing the Efficacy and Side Effects of Propofol and Midazolam Plus Pethidine among Patients Undergoing Esophagogastroduodenoscopy at Rizgary Hospital in Erbil, Iraq

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ABSTRACT

Background: *Propofol and midazolam plus narcotics continued to be the most commonly used sedative agents in Esophagogastroduodenoscopy (EGD).*
Objective: *This study aimed to compare the safety and quality of sedation by monitoring vital signs, awareness, depth of anesthesia, length of procedure, and post-sedation side effects of propofol and midazolam plus pethidine among patients who underwent EGD at Rizgary Hospital, in Erbil, Kurdistan region of Iraq.*
Patients and Methods: *Forty (40) patients who were scheduled to undergo EGD were randomized into two equal groups, each group included twenty (20) patients. Group I received propofol as a single agent. Group II received midazolam plus pethidine. Several parameters were measured during and after the procedure. Also, the post-sedation side effect profiles of both drug regimens were recorded.*
Results: *Propofol significantly lowered several parameters such as blood pressure, pulse rate, respiratory rate, and SpO2. In contrast, midazolam plus pethidine significantly increased all the mentioned parameters except SpO2 which was slightly lowered. Propofol produced deep sedation with a short procedure time, whereas midazolam plus pethidine produced moderate sedation with a longer procedure time. The incidence of post-sedation side effects was lower in the propofol group compared to the midazolam plus pethidine group.*
Conclusions: *Propofol is preferred over midazolam/pethidine in inducing sedation during EGD as it was associated with a shorter duration of procedures, less fluctuation in pulse rate and blood pressure, less awareness, deeper sedation, and fewer post-sedation side effects such as nausea and vomiting.*

Keywords: *Gastrointestinal endoscopy, Esophagogastroduodenoscopy, Sedation, Propofol, Midazolam, Cross-sectional studies*

1. INTRODUCTION

Throughout the past few decades, there has been a sharp increase in the number of minimally invasive procedures that are carried out outside of surgical rooms (Sheta, 2010), because such procedures were uncomfortable to bear, this allowed physicians to start using sedation to perform them, a clear example of this is using sedative services in the gastrointestinal (GI) endoscopy (Tetzlaff et al., 2014). Although some patients can tolerate endoscopic procedures even without sedation, the majority of patients require sedation for a better outcome, thus sedation nowadays has been used consistently in endoscopic procedures (Sipe et al., 2002). Efficient sedation and analgesia during endoscopy not only satisfy patients by relieving their pain and anxiety from the procedure but also satisfy physicians and typically aids in facilitating the procedure completion time (Tobias & Leder, 2011). The intensity of patient stimulation and pain during GI endoscopic procedures varied widely, as a result, different agents were used for inducing sedation. Most patients could successfully be sedated during Esophagogastroduodenoscopy (EGD) with a combination of an intravenous (IV) benzodiazepine and an opioid or using IV propofol (Goulson & Fragneto, 2009). Using IV midazolam was more favorable compared to other benzodiazepines due to its extra advantages including better-controlled sedation with a rapid recovery time, and rapid onset which may be linked to greater patient acceptability (McQuaid & Laine, 2008; Rosen & Rosen, 1998). As endoscopic procedures became more complicated, the desire for stronger sedation increased (Allen, 2017), thus for such complicated procedures, and for patients who had a history of drug addiction or who were difficult to sedate typically needed deep sedation or general anesthesia, propofol is a viable choice for them (Goulson & Fragneto, 2009). Different studies were conducted previously to compare the effects of propofol and midazolam in different operations, while only a few studies compared propofol as a single agent versus midazolam plus pethidine in patients undergoing esophagogastroduodenoscopy (EGD), but none of these studies were conducted in Erbil, Iraq. This study aimed to compare the safety and quality of sedation by monitoring vital signs, awareness, depth of anesthesia, length of procedure, and side effect profile of propofol and midazolam plus pethidine among

patients who underwent non-emergent EGD at Rizgary Teaching Hospital, in Erbil, Kurdistan region of Iraq.

2. METHODOLOGY

This was a randomized clinical trial conducted during the period from the 24th of October to the 5th of December, 2022 at the Department of Gastroenterology and Hepatology in Rizgary Teaching Hospital. A total of forty patients enrolled in this study between October 2022 and December 2022. The included patients were undergoing diagnostic outpatient esophagogastroduodenoscopy (EGD) at Rizgary Teaching Hospital Department of Gastroenterology and Hepatology to investigate their upper gastrointestinal tract with or without taking a biopsy. Included patients aged from 15 to 73 years, in which 24 (twenty-four) of whom were females and 16 (sixteen) were males and were randomly allocated to receive either intravenous midazolam plus pethidine or propofol as a sedative agent during the endoscopy.

Inclusion criteria

All the patients enrolled in this study have met the following criteria:

1. Male or Female aged 15 to 75 years.
2. Patients scheduled to undergo outpatient EGD.
3. No previous allergy to anesthetics.
4. Willing to participate in this study.

Exclusion criteria

Patients were excluded from enrollment if any of the following criteria were present:

1. Children and adolescents aged less than 15 years, or elder patients aged above 75 years.
2. Patients scheduled to undergo other endoscopic procedures such as colonoscopy and ERCP, or those undergoing inpatient EGD.
3. Allergy to egg or soy products.
4. Contraindications to sedation.
5. Refusing to be a part of this study.

Study groups and intervention:

The 40 patients were randomly assigned into two groups with 20 patients in each:

Group I : Included patients who received I.V. propofol as a single agent, which was delivered undiluted as a (10mg/ml) solution. The total dose of propofol given to each patient during this study was in the range of (70-200mg), which was administered by nurses as a bolus loading dose and maintenance doses to keep an adequate level of sedation during the period of the procedure. The loading dose usually was in the range of (30-50mg), followed by successive doses with each push of (10-20mg) with a minimum of 20 to 30 seconds passing between each dose (Moon, 2014) , for a total of (20-150mg). All the patients in this group were on supplemental oxygen (5L/min) through a nasal cannula.

Group II: Included patients who received midazolam plus pethidine intravenously. Midazolam was diluted by using 0.9% normal saline from a (5mg/ml) solution to (1mg/ml) solution, and it was administered by nurses in a range of (2-6mg) for each patient. The loading dose was in the range of (2-4mg) followed by a maintenance dose with each push of (1-2 mg) for a total of (1-4mg). Pethidine was administrated to all the patients who received midazolam. It was diluted to a (10mg/ml) solution. The total dose of pethidine given to each patient was in the range of (20-75m).

Data collection:

Data were collected using a pre-constructed data collection sheet prepared by the authors Data collection was performed through full history taking and thorough clinical examination.

Preoperatively we reported the demographic characteristics; patient's age, social history (smoking & alcohol consumption). medical history of chronic diseases which was taken into account to individualize the best dose for each patient in both groups.

Additionally we reported other data including past surgical history, allergies, and history medication use. This history-taking helped to individualize the dose of the sedative agent for each patient.

Perioperative assessment: vital signs were checked and reported included blood pressure (checked by an automated sphygmomanometer), pulse rate and SpO2 (checked by a pulse oximeter) and respiratory rate was measured by counting the patient's breath per minute.

Also, two parameters (awareness and depth of anesthesia (DoA)) were measured during the procedure. We used the traditional way of measuring the DoA by monitoring the change in the mean arterial blood pressure and pulse rate. To make it easier to compare both groups in terms of DoA, we gave (2,4,6,8,10) scores according to the changes. The larger the number the deeper the sedation, resulting in more relaxed (stable) patients. While for awareness, we used a 10 points scale from 1 – 10 . Numbers were given to each patient by observing respiration patterns, eyelash reflexes, movements, and responses to orders. The larger the numbers, the higher the awareness.

Post-operatively: patients were followed up looking for vital signs which were usually measured at 30 minutes to 1 hour after the end of the procedure, and at that time patients were asked about any side effect that might developed, so that all of the possible side effects from the sedative agents were recorded such as; nausea, vomiting, headache, dizziness, blurred vision, and any other possible side effect.

Ethical approval:

Verbal and signed consents were obtained from all participants before they were enrolled in the study. The study protocol , intervention and procedures were clearly discussed and explained to all patients. Data of the patients were kept confidentially; names of the patients and other personal information were hided and replaced with specific codes and serial numbers.

Statistical analysis

Data were managed and processed using statistical software with database and statistical analysis utility. The Statistical package for social sciences (SPSS) software for windows version 28, used for this purpose . Quantitative variables were presented as mean ± standard deviation (SD) or standard error of mean (SE). Student's t-test for 2 independent samples used to compare mean value of a variable between the two studied groups. The difference was considered significant whenever the (P. value was ≤ 0.05).

3. RESULTS

A total of 40 patients were selected according to this study's inclusion and exclusion criteria, and they were randomized into two groups (group I & II), each of which included 20 patients. Group I received propofol, while group II received midazolam plus pethidine. Generally, 60% (24) of the total included patients (40) in this study were females who were randomly distributed over the study groups. Health habits such as smoking and alcohol consumption were reported during the data collection, and results showed that the majority of the participants in group I (55%) were smokers, and the rest (45%) were non-smokers or alcoholics, while the majority of group II (70%) were non-smokers or alcoholics, (20%) were only smokers, and (10%) were smokers and alcoholics, as shown in (**Table 1**). The mean age ± SD in group I was (40.5 ± 15.408) years, while in group II was (37.4 ± 14.440) years, indicating that patients in group II were slightly in a younger age range compared to group I. The mean time required to complete procedures ± SD in group I was (6.05 ± 2.910) minutes, while in group II was (8.95 ± 4.622) minutes, indicating that using propofol facilitated the endoscopic procedures. The mean loading doses ± SD for propofol and midazolam were (33.5 ± 7.451) and (2.5 ± 0.606) milligrams, respectively, which showed that midazolam was used in small doses because it was combined with a second agent (pethidine) that worked synergistically with midazolam. In group I, all the patients (100%) received maintenance doses with a mean ± SD of (78 ± 39.416) milligrams, while in group II, only 13 patients (65%) required maintenance doses with a mean of (1.84 ± 0.863) milligrams of midazolam, (**Table 2**). In group I, during the procedure, a systolic blood pressure ≤ 100mmHg was documented in 10 (50%) patients, a diastolic blood pressure ≤ 60mmHg was documented in 14 (70%) patients, and an oxygen saturation < 95% was documented in 4 (20%) patients. Also, the pulse rate reached less than 60bpm in 5 (25%) patients, and the respiratory rate reached less than 12BPM in 14 (70%) patients. Whereas in group II, 18 (90%) out of 20 (100%) patients had a systolic blood pressure≥140mmHg, and 12 (60%) of them had a diastolic blood pressure≥90mmHg as well. Also, a pulse rate ≥ 100bpm was documented in all the patients except one which was 96bpm. While the respiratory rate and SpO2 were in the normal range. Generally, a mean ± standard error and P values were calculated for all the

parameters, and the results revealed statistically significant differences in all the parameters between both groups during the procedure (P value < 0.05), in which for the propofol group, the mean PR, RR, SpO2, SBP, and DBP ± SE during the procedure were (65.9±1.8), (11.15±0.28), (94.6±0.85), (104.7±2.6), and (55.7±2.2), respectively. While in midazolam plus pethidine (group II), they were (116.8±2.1), (14.15±0.4), (97.9±0.4), (164.6±4.9), and (87.1±2.4), respectively. In group I, the mean PR, SBP, and DBP ± SE after 30 minutes to one hour of the procedure were (77.3±1.9), (122.5±3.9), and (67.5±1.9), respectively. While, in group II, they were (96.4±3.5), (136.3±4.5), and (77±2.6), respectively. These results revealed statistically significant differences in PR, SBP, and DBP between both studied groups after 30 minutes to one hour of the procedure, (P value=0.000, 0.023, and 0.022, respectively). The mean RR and SpO2 ± SE were compared after (30-60) minutes of the procedures for both groups, and the comparison revealed no statistically significant differences (P value= 0.33 and 1, respectively). Comparing the results of table 3 which show the values of different parameters during the esophagogastroduodenoscopy procedure (after induction of the sedative agents), and the results of table 4 which show the values of the same parameters after (30-60) minutes from the procedure (in the recovery room, in which most of the parameters nearly returned back to normal), reveals that during the procedure group I reduced all the parameters (PR, RR, SpO2, SBP, and DBP), while group II increased all the parameters except SpO2 which was slightly lowered, (**Table 3 and Table 4**). Additionally, statistically significant differences between group I and group II were found in both awareness and DoA, (P value=0.000). The mean awareness ± SE for group I (propofol) and group II (midazolam plus pethidine) were (1.6±0.15) and (4.9±0.26) respectively. While the mean DOA ± SE were (7.55±0.16) and (4.1±0.3) for group I and II, respectively. This data revealed that group I had a deeper sedation level with less awareness of surroundings compared to group II who had a moderate depth of sedation during the procedure, as shown in (**Table 5**). As shown in (**Table 6**), group II was associated with a higher incidence of post-sedation side effects including; nausea (35%), vomiting (10%), headache (20%), dizziness (45%), and blurred vision (15%). While in group I, none of the included patients suffered from vomiting or headache. Generally, propofol was associated with a lower incidence of

post-sedation side effects, and according to this study, propofol's most predominant post-sedation side effect was dizziness (35%).

Table 1 . distribution of gender and health habits (smoking and alcohol consumption) among participants in both studied groups

Variable		Group I (n=20)		Group II (n=20)	
		No.	%	No.	%
Gender	Male	12	60.0	4	20.0
	Female	8	40.0	16	80.0
Health habits	Only smokers	11	55.0	4	20.0
	Smokers & alcoholics	0	0.0	2	10.0
	None	9	45.0	14	70.0

Table 2 . Comparison of patient's age , duration of procedures, loading dose, maintenance dose and total dose in both studied groups

Variables	Group I (n=20)			Group II (n=20)		
	Mean	SD	Ranges	Mean	SD	Ranges
Age (years)	40.5	15.408	17-70	37.4	14.44	15-73
Duration of procedures (min)	6.05	2.91	3 - 15	8.95	4.622	4 - 20
Loading dose (mg)	33.5	7.451	30-50	2.5	0.606	2 – 4
Maintenance dose(mg)	78	39.416	20-170	1.84*	0.863	1 – 4
Total dose (mg)	111.5	36.31	70-200	3.7	1.031	2 - 6

*Maintenance dose in group 2 reported for 13 patients only. min: minute

Table 3. Comparison of pulse rate, respiratory rate, SpO2, systolic and diastolic blood pressure during the procedure in both studied groups

Parameters	Group I (n=20)		Group II (n=20)		P. value
	Mean	SE	Mean	SE	
Pulse rate (pulse/min)	65.9	1.80	116.8	2.1	< 0.001
Respiratory rate (breaths/ min)	11.2	0.28	14.2	0.4	< 0.001
SpO2 (%)	94.6	0.85	97.9	0.4	0.005
Systolic BP (mmHg)	104.7	2.6	164.6	4.9	< 0.001
Diastolic BP (mmHg)	55.7	2.2	87.1	2.4	< 0.001

BP: blood pressure

Table 4 . Comparison of pulse rate, respiratory rate, SpO2, systolic and diastolic blood pressure after (30-60) minutes of the procedure in both studied groups.

Parameters	Group I (n=20)		Group II (n=20)		P. value
	Mean	SE	Mean	SE	
Pulse rate (pulse/min)	77.3	1.90	96.4	3.50	<0.001
Respiratory rate (breaths/ min)	12.8	0.20	13.2	0.30	0.330
SpO2 (%)	98.6	0.16	98.6	0.18	1.000
Systolic BP (mmHg)	122.5	3.90	136.3	4.50	0.023
Diastolic BP (mmHg)	67.5	1.90	77.0	2.60	0.022

BP: blood pressure

Table 5 . Comparison of awareness and depth of sedation between the studied groups

Parameters	Group I (n=20)		Group II (n=20)		P. value
	Mean	SD	Mean	SD	
Awareness	1.6	0.15	4.9	0.26	<0.001
Depth of anesthesia	7.55	0.16	4.1	0.3	<0.001

Table 6. Distribution of Post-sedation side effects in Group I and II.

Side effects	Group I (n=20)		Group II (n=20)	
	No.	%	No.	%
Nausea	1	5.0	7	35.0
Vomiting	0	0.0	2	10.0
Headache	0	0.0	4	20.0
Dizziness	7	35.0	9	45.0
Blurred vision	1	5.0	3	15.0

4. DISCUSSION

Esophagogastroduodenoscopy (EGD) has been a commonly utilized diagnostic and therapeutic procedure in the management of GI illnesses which can be completed within a few minutes. To minimize patients suffering during the procedure, many drugs with different regimens are available to induce sedation and analgesia including; topical anesthetics, benzodiazepines with/without opioids, or propofol (Barriga et al., 2008). Throughout this study, we compared the efficacy and safety of Propofol and midazolam plus pethidine in terms of the depth of anesthesia, awareness, duration of the procedure, vital signs, and side effect profile. Both drug regimens were administered by nurses while supervised by endoscopists. In general, monitoring patients who received propofol during the procedure was more difficult for nurses than monitoring those patients who received midazolam plus pethidine, because propofol was producing deep sedation (third level of sedation), so they had to keep patients at that level and prevent patients from passing to level four (general anesthesia), whereas midazolam plus pethidine produced moderate sedation (level two) which was far by two levels from producing GA, thus less strict monitoring required in group II. Generally, group I (who received propofol) were stable, their pulse rate and blood pressure didn't change frequently, their movements during the procedure were less, and they had a very good depth of anesthesia with no or slight awareness. While those patients who received midazolam plus pethidine, their pulse rate, and blood pressure were fluctuating, and the overall patients' conditions were not stable during the procedure, they were moving too much, thus propofol was preferred from this point due to its better depth of anesthesia and less awareness, that's why in group I, patients were more relaxed thus gastroenterologists were more satisfied during the procedure so that the time required to complete the procedure (6.05 ± 2.910) was less in comparison to (group II) midazolam plus pethidine (8.95 ± 4.622), which agrees the results of (Sipe et al., 2002; Tabiri et al., 2018).

Apnea can result from propofol induction. Due to the suppression of the hypercapnic ventilatory drive, propofol results in a dose-dependent respiratory depression (Folino et al., 2022), and that's why the majority of the patients in group I developed "transient apnea" after induction of propofol, in which the SpO2 reduced to less than (90%), but normalized

immediately with administering oxygen (5ml/min) through a nasal cannula, while in group II, none of the patients developed transient apnea, thus none of them were on nasal oxygen, and this was a positive point for group II. Due to propofol's ability to inhibit the SNS (sympathetic nervous system) and impair the baroreflex regulation (Tsikas et al., 2015), a significant reduction in systolic and diastolic blood pressure was recorded in (55%) of patients after induction of propofol with a MABP (mean arterial blood pressure) of (≤100/60mmHg), also a reduction in pulse rate to less than 60bpm was recorded in (25%) of patients from group I. Midazolam, when administered intravenously, has dose-related impacts on the somato-sympathetic reflexes, by which at lower doses, it activates the reflex sympathetic activity, whereas, at higher doses, it suppresses the somato-sympathetic reflexes (Iida et al., 2007), and because in our study, we administered midazolam as a bolus loading dose ± SD of (2.5 ± 0.606), which considered as a low dose, thus midazolam augmented the reflex sympathetic activity, resulting in increased MABP to (≥114/90mmHg) in (55%) of patients in group II, also caused an elevation of pulse rate relatively in all the patients, and this elevation of the pulse rate supports the results of (Oh et al., 2013). Thus in our study, the incidence of hypotension, bradycardia, and hypoxemia were significantly higher in patients who underwent sedation with propofol than in those patients who underwent sedation with midazolam plus pethidine which supports the results of (Hajiani et al., 2018), while shows a contrast to (Tsai et al., 2015) who reported that, there is no significant difference in the occurrence of hypotension, bradycardia, or hypoxemia between both drug regimens. Our results revealed that the incidence of postoperative nausea and vomiting (PONV) was less with administering propofol compared to midazolam plus pethidine. In general, propofol was associated with fewer post-sedation-related side effects, but "dizziness" was increasingly reported, while in group II, different side effects such as nausea, vomiting, headache, and dizziness were frequently reported after 30-60 minutes of the procedures. Thus, in terms of post-sedation side effects, propofol was relatively safer and associated with fewer post-sedation side effects compared to midazolam plus pethidine.

5. CONCLUSIONS

Results show that using propofol for sedation in esophagogastroduodenoscopy was preferred by endoscopists as it was associated with a shorter duration of procedures, less fluctuation in pulse rate and blood pressure, less awareness, and deeper sedation in comparison to midazolam plus pethidine. Propofol was associated with a significant reduction in mean arterial blood pressure and pulse rate, while midazolam plus pethidine elevated both parameters. The incidence of PONV and other post-sedation side effects were lower in propofol group than in midazolam plus pethidine group. Hence we recommend conducting further studies with a larger sample size and more similar patient profiles in regard to their age and medical conditions (such as enrolling only ASA class I or II patients) so that the comparison will be easier. Additionally, dealing with such similar cases will eliminate or decrease the role of chance in measuring the parameters, thus more accurate results will be obtained.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients enrollment were in accordance with Declaration of Helsinki of World Medical Association , 2013 for the ethical principles of researches involving human. Signed informed consent was obtained from each participant and data were kept confidentially.

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