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RESEARCH ARTICLE

Evaluation of Different Sedative Approaches for Cirrhotic Patients during Upper Gastrointestinal Endoscopy

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Abstract

Background: Sedation and analgesia comprise important elements during endoscopic examinations to sedate and achieve the comfort of patients but patients with liver cirrhosis could be at increased risk to develop complications which are related to sedation as most sedative drugs are metabolized by the liver. **Aim of the work**: The aim of the present study is to evaluate different sedative approaches for cirrhotic patients during upper gastrointestinal endoscopy (UGIE). **Patients and methods**: This study was carried out on 99 patients with liver cirrhosis referred for diagnostic and / or therapeutic UGIE. They were divided equally according to the scheduled pre-endoscopic sedation into three groups: Midazolam plus Fentanyl group, Propofol plus Fentanyl group and Ketamine group. All patients were subjected to detailed history taking, thorough physical examination, routine laboratory investigations, abdominal ultrasound and ECG, with monitoring of mean arterial blood pressure (MAP), heart rate and oxygen saturation (before, during and after endoscopy) to assess safety, efficacy and recovery time of the used sedative drugs.

Results: Our results revealed that there was no statistically significant difference between the studied groups regarding age, weight, sex and Child-Pugh score distribution. Considering MAP and heart rate; there was a high statistically significant difference between Ketamine group and the other two groups during and after the procedure ($P< 0.001$). Efficacy of propofol plus fentanyl sedation was 100 % followed by midazolam plus fentanyl group and Ketamine group (efficacy was 97 % and 91 % respectively). Propofol plus fentanyl group had the shortest recovery time (11.4±2.6 minutes) followed by midazolam plus fentanyl group (23.8±5.6 minutes) and Ketamine group (31.3±6.0 minutes).

Conclusion: Sedation with propofol plus fentanyl for patients with liver cirrhosis undergoing UGIE was safer, more efficacious with better comfort for patients as well as endoscopists and had shorter recovery time with early discharge than midazolam plus fentanyl and Ketamine sedation.
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Introduction:

Patients with liver cirrhosis are commonly referred for UGIE for diagnostic and / or therapeutic purposes either for banding or injection sclerotherapy. These endoscopic procedures can cause pain or discomfort, so sedation is recommended to minimize anxiety and to perform the examination safely. Sedation and analgesia comprise important elements during endoscopic examinations to sedate and achieve the comfort of the patient during the procedure and also increases willingness to undergo a repeat procedure but patients with liver cirrhosis could be at increased risk to develop complications which are related to sedation as most sedative drugs are metabolized by the liver **(1).**

Various types of sedation and analgesia are used during UGIE. However, there is no standard sedation regimen for UGIE **(2).**

Patients and Methods:

This study was carried out in the endoscopy unit of Internal medicine and Tropical medicine departments in collaboration with anesthesia department, Zagazig university hospital in the period from August 2013 to February 2014 on 99 patients with liver cirrhosis referred for diagnostic and / or therapeutic UGIE. Patients were divided equally into three groups according to scheduled pre-endoscopic sedation as follow:

- Midazolam plus Fentanyl group: included 33 patients who received midazolam slow I.V (0.05 mg/kg with additional doses of 1 mg every 2 minutes when necessary until the maximum dose 0.1 mg/kg or 10 mg is reached) plus fentanyl 50 mcg in a single I.V dose **(3).**

- Propofol plus Fentanyl group: included 33 patients who received propofol slow IV (0.25 mg/kg with additional doses of 20 to 30 mg every 30 to 60 seconds when necessary until the maximum dose 400 mg is reached) plus fentanyl 50 mcg in a single I.V dose **(3).**

- Ketamine group: included 33 patients who received ketamine slow IV (0.5 mg/kg with additional dose 0.25-0.5 mg/kg when necessary until maximum dose 2 mg/kg is reached **(4)**.

Inclusion criteria:
Child-Pugh score A or B patients who presented for diagnostic and / or therapeutic UGIE. A written informed consent was taken from all participants.

Exclusion criteria:
Allergy or previous adverse reactions to the used drugs, age lesser than 18 or older than 65 years, Child-Pugh C score, need for emergency endoscopy, hemodynamically unstable patients, significant cardiopulmonary disease, hepatic encephalopathy, active prescription of sedatives or narcotics or drug abuse one week prior to the endoscopy time and alcoholics **(3).**

All participants in the study were subjected to detailed history taking, thorough physical examination, laboratory work up (complete blood count, liver function tests, coagulation profile, renal function tests and random blood sugar), abdominal ultrasound and ECG with assessment of MAP, heart rate, oxygen saturation before, during and after endoscopy, assessment of the conscious level according to Observer's Assessment of Alertness/Sedation Scale (OAAS), assessment of efficacy of the sedative drugs used in the study, the ease of the procedure by the endoscopist, cooperation of the patient (comfort of the endoscopist) and comfort of the patient by watching patient's facial expression and gagging reflex, assessment of postendoscopy conscious level and recovery time.

Observer's Assessment of Alertness/Sedation Scale (OAAS) (5):

Responsiveness	Speech	Facial expression	Eyes	Score
Responds readly to name	Normal	Normal	Clear with no ptosis	**5**
Lethargic response to name	Mild Slowing or thickening	Mild relaxion	Glazed or mild ptosis	**4**
Responds only after name is called loudly and/or repeatedly	Slurring or proeminent slowing	Marked relaxion	Glazed and marked ptosis	**3**
Responds only after mild prodding or shaking	Few recognizable words	-	-	**2**
Does not respond to mild prodding or shaking	-	-	-	**1**

Efficacy:

The proportion of complete procedures performed by using the initial proposed sedation scheme. The sedation scheme was considered ineffective when the procedure was interrupted by agitation or intolerance by the patient despite the maximum sedative dose **(3).**

Recovery time:

It is the time lapse between the end of the endoscopic procedure and hospital discharge **(3).**

Statistical Analysis:

Data were collected, entered and checked to SPSS version 15. Data were expressed as mean ± standard deviation ($\bar{X}$ ± SD) in quantitative variables. Number and percentage for qualitative variables, F test (ANOVA). Also paired t-test and least significant difference (LSD) were used for analysis of data. P-value < 0.05 was considered as significant and P-value < 0.001 was considered as highly significant.

Results:

Table (1): Demographic data of the studied groups.

Variable	Midazolam+fentanyl group N=33		Propofol+fentanyl group N=33		Ketamine group N=33		*P*	
	Mean ± SD		Mean ± SD		Mean±SD			
Age Range(years)	54.7±5.7 45 – 64		55.6±5.5 43 – 64		56.3±6.1 37 – 64		NS 0.52	
Weight Range (kg)	76.4±6.5 59 – 87		76.2±6.2 63 – 87		77.5±7.9 54 – 98		NS 0.7	
Sex	No.	%	No.	%	No.	%	X^2	*P*
Male	21	63.6	20	60.6	23	69.7	0.62	NS 0.71
Female	12	36.4	13	39.4	10	30.3		

Table (2): Child-Pugh score distribution among the studied groups.

Child-Pugh score	Midazolam+fentanyl group N=33		Propofol+fentanyl group N=33		Ketamine group N=33		X^2	*P*
	No.	%	No.	%	No.	%		
A	19	57.6	21	63.6	26	78.8	3.55	NS 0.16
B	14	42.4	12	36.4	7	21.2		

Table (3): Means ± SD of MAP and heart rate among the studied groups.

MAP	Midazolam+fentanyl group N=33	Propofol+fentanyl group N=33	Ketamine group N=33	*P*
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Before	89.8±10.2	89.7±10.3	89.9±10.1	NS 0.96
Range (mm Hg)	70 – 106.6	70 – 106.6	70 – 106.6	
During	82.7±7.8	82.9±7.9	97.8±8.3	HS <0.001
Range (mm Hg)	70 – 96.6	70 – 96.6	73.3 – 116.6	
After	80.2±7.6	80.7±7.6	96.5±7.9	HS <0.001
Range (mm Hg)	63.3 – 93.3	66.6 – 93.3	70 – 110	
Heart rate	**Midazolam+fentanyl group** N=33	**Propofol+fentanyl group** N=33	**Ketamine group** N=33	P
	Mean ± SD	Mean ± SD	Mean ± SD	
Before	79.7±8.6	80.9±8.1	80.4±11.2	NS 0.84
Range (beat/min)	68- 94	68 – 94	62 – 96	
During	72.9±7.9	71.2±7.6	86.6±14	HS <0.001
Range (beat/min)	62 – 90	61 – 88	68 – 106	
After	69.9±7.7	68.9±6.1	85.1±15.2	HS <0.001
Range (beat/min)	60 – 88	54 – 78	70 – 100	

Table (4): Least Significant Difference (LSD) of means ± SD of MAP during and after the procedure among the studied groups.

Group	Compared groups	MAP during procedure (mmHg)	MAP after procedure (mmHg)
Midazolam+fentanyl	**Propofol+fentanyl**	NS	NS
	Ketamine	HS < 0.001	HS < 0.001
Propofol+fentanyl	**Midazolam+fentanyl**	NS	NS
	Ketamine	HS < 0.001	HS < 0.001
Ketamine	**Midazolam+fentanyl**	HS < 0.001	HS < 0.001
	Propofol+fentanyl	HS < 0.001	HS < 0.001

Table (5): LSD of means ± SD of heart rate during and after the procedure among the studied groups.

Group	Compared groups	Heart rate during procedure (beat/min)	Heart rate after procedure (beat/min)
Midazolam+fentanyl	**Propofol+fentanyl**	NS	NS
	Ketamine	HS < 0.001	HS < 0.001
Propofol+fentanyl	**Midazolam+fentanyl**	NS	NS
	Ketamine	HS < 0.001	HS < 0.001
Ketamine	**Midazolam+fentanyl**	HS < 0.001	HS < 0.001
	Propofol+fentanyl	HS < 0.001	HS < 0.001

Table (6): Means ± SD of oxygen saturation among the studied groups.

Oxygen saturation	Midazolam+fentanyl group N=33	Propofol+fentanyl group N=33	Ketamine group N=33	*P*
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Before	97.5±1.4	97.1±1.4	97.4±1.4	NS 0.7
Range (%)	95- 99	96 – 99	95 – 99	
During	94.7±1.7	93.9±1.8	95.2±1.8	NS 0.3
Range (%)	93 -98	94 – 98	93 – 99	
After	92.8±2.9	92.6±2.2	93.1±2.4	NS 0.14
Range (%)	85 -97	92 – 98	92 – 98	

Table (7): Efficacy among the studied groups.

Efficacy	Midazolam+fentanyl group N=33		Propofol+fentanyl group N=33		Ketamine group N=33		X^2	*P*
	No.	%	No.	%	No.	%		
Efficacious	32	97	33	100	30	91	3.19	NS 0.2
Non-efficatious	1	3	0	0	3	9		

Table (8): Comfort of endoscopist and patients among the studied groups.

Comfort of endoscopist	Midazolam+fentanyl group N=33		Propofol+fentanyl group N=33		Ketamine group N=33		X^2	*P*
	No.	%	No.	%	No.	%		
Comfortable	32	97	33	100	30	91	2.95	NS 0.2
Uncomfortable	1	3	0	0	3	9		
Comfort of patient	**Midazolam+fentanyl group N=33**		**Propofol+fentanyl group N=33**		**Ketamine group N=33**		X^2	*P*
	No.	%	No.	%	No.	%		
Comfortable	32	97	33	100	30	91	2.95	NS 0.2
Uncomfortable	1	3	0	0	3	9		

Table (9): Post-endoscopy conscious level* among the studied groups.

OAAS score	Midazolam+fentanyl group N=33		Propofol+fentanyl Group N=33		ketamine group N=33		X^2	*P*
	No.	%	No.	%	No.	%		
Score (5)	31	94	33	100	30	91	3.91	NS 0.22
Score (3-4)	2	6	0	0	3	9		
Score < (3)	0	0	0	0	0	0		

(*)According to Observer's Assessment of Alertness/Sedation Scale (OAAS)

Table (10): Means ± SD of the recovery time among the studied groups.

Recovery time	Midazolam+fentanyl group N=33	Propofol+fentanyl group N=33	Ketamine group N=33	*P*
	Mean ± SD	Mean ± SD	Mean ± SD	
Recovery time	23.8±5.6	11.4±2.6	31.3±6.0	HS <0.001
Range (Minutes)	15 – 34	10 – 15	19 – 41	

Discussion:

Upper gastrointestinal endoscopy is the method of choice for diagnosis and treatment of esophageal and gastric varices. Sedation is required in endoscopic procedures to increase patient satisfaction and willingness to repeat the procedure **(6).**

There are few studies assessing sedation in cirrhotic patients during UGIE **(7)**, so we performed our study in a trial to assess the safety, efficacy and recovery time of different sedative drugs used during diagnostic and /or therapeutic UGIE in patients with liver cirrhosis.

Our study showed that there was no statistically significant difference between the studied groups regarding age, sex, weight and Child–Pugh classification score. These factors may affect the dose of the drug and its related complications (**8)**.

We reported a high statistically significant difference among the three groups regarding MAP and heart rate during and after the procedure ($p < 0.001$), but there was no statistically significant difference between the studied groups regarding oxygen saturation (p=NS).

In midazolam plus fentanyl group; all patients had normal ranges of MAP, heart rate and oxygen saturation apart from two patients had mild hypotension after the procedure (MAP was 63.3 mmHg in both patients) that did not require treatment and one patient had mild hypoxemia after the procedure (oxygen saturation was 85%) that was corrected by using oxygen mask. This was explained by **Fukuda et al. (9)** who reported that midazolam causes central respiratory depression and hypotension due to reduction in systematic vascular resistance. Also **Tolia et al. (10)** reported that fentanyl causes respiratory depression and hypotension due to vagal stimulation.

Correia et al. (3) went in concordance with our result and recorded 7 patients out of 110 patients had mild hypotension and 4 patients had mild hypoxemia in midazolam plus fentanyl group when they compared safety of midazolam plus fentanyl versus propofol plus fentanyl in 210 patients with liver cirrhosis undergoing UGIE **.**

In contrast to our result**; Barriga et al. (11)** reported serious hypotension in 16 patients required saline solution infusion out of 480 patients received midazolam plus fentanyl, also serious hypoxemia occurred in one patient who managed with endotracheal intubation and mechanical ventilation, this may be attributed to their use of a higher dose of midazolam (0.1 mg/kg) than the dose we used in our study (0.05 mg/kg) and higher number of patients included in their study.

Our study showed that all patients in propofol plus fentanyl group had normal ranges of MAP, heart rate and oxygen saturation apart from one patient had mild hypotension after the procedure (MAP was 66.6 mmHg) that did not require treatment and one patient had mild bradycardia after the procedure (heart rate was 54 beat/min) that was corrected by administration of atropine. **Favetta et al. (12)** attributed hypotension and bradycardia produced by propofol to peripheral vasodilatation, decrease sympathetic outflow and depression of myocardial contractility. Also fentanyl causes drop in blood pressure and heart rate due to vagal stimulation **(10)**.

Correia et al. (3) agreed with our results and reported mild hypotension in 3 patients and mild bradycardia in 3 patients out of 100 patients received propofol plus fentanyl. In contrast, **Moerman et al. (13)** recorded serious hypotension, bradycardia and hypoxemia in 14 % out of 50 patients received propofol plus fentanyl. This may be related to a higher dose of propofol used in that study (1mg/kg) than the dose we used in our study (0.25 mg/kg).

Considering Ketamine group; all patients had normal ranges of MAP, heart rate and oxygen saturation except one patient had mild hypertension during the procedure (MAP was 116.6 mmHg) and returned to normal level after

the procedure without treatment. Also two patients had mild tachycardia during the procedure (heart rate was 104 and 106 beat/min) but returned to normal level after the procedure without treatment, this was related to the sympathetic stimulatory effect of Ketamine which leads to rise in blood pressure and heart rate **(14)**. In contrast, **Spearman et al. (15)** recorded serious hypertension and tachycardia in 18% of patients, this may be attributed to a higher dose of Ketamine used in their study (1mg/kg) than the dose we used in our study (0.5 mg/kg).

As regard the efficacy of the sedative drugs used in our study and comfort of patients as well as endoscopists; propofol plus fentanyl group recorded the best results followed by midazolam plus fentanyl and Ketamine groups, as all patients in propofol plus fentanyl group had a complete endoscopic procedure with initially proposed sedation scheme, while endoscopic procedure was hardly performed in one patient in midazolam plus fentanyl group and in three patients in Ketamine group even with maximum doses of midazolam and Ketamine respectively, as these patients became agitated with frequent gagging and they did not tolerate the procedure despite of sedation. However, there was no statistically significant difference among the studied groups regarding efficacy, comfort of patients and endoscopists.

Correia et al. (3) agreed with our finding and reported that all patients in propofol plus fentanyl group had a complete endoscopic examination with initially proposed sedation scheme, while in midazolam plus fentanyl group 13 of 110 procedures could not be performed even with maximum dose of midazolam because of agitation. However, they reported a high significant difference between both groups regarding the efficacy (100% vs. 88.2 % respectively, $p < 0.001$), this may be related to higher number of patients included in this study. Also **McQuaid and Laine, (6)** finding goes well with our result as they reported that propofol sedation provided higher level of satisfaction for both patients and endoscopists than did midazolam for moderate sedation in UGIE. Also **Green and Krauss (16)** reported that Ketamine is not recommended as a mono-therapeutic agent for endoscopic examinations in adults because the pharyngeal reflexes are maintained so patients may be agitated and had frequent gagging.

On comparing post-endoscopy conscious level; we found that all patients were conscious after the endoscopic procedure. However, in propofol plus fentanyl group all patients gained score 5 according to OAAS Scale shortly (2-4 minutes) after the endoscopic procedure while two patient in midazolam plus fentanyl group and three patients in Ketamine group gained score 5 after 10 - 15 minutes post endoscopy.

A randomized study by **Riphaus et al. (17)** reported a significantly faster recovery time and quicker recovery of psychomotor function after sedation with propofol on comparing propofol versus midazolam during UGIE. Moreover, midazolam may also precipitate the probable worsening of hepatic encephalopathy and this was observed by **Assy et al. (18)** who demonstrated that most cirrhotic patients with subclinical encephalopathy became worse after midazolam administration. However, propofol does not trigger acute deterioration of minimal encephalopathy and this was proved by a study performed by **Amoros et al. (19)** who found that even deep sedation with propofol did not precipitate subclinical or overt hepatic encephalopathy in cirrhotic patients.

Regarding the recovery time; there was a high statistically significant difference among the studied groups with the shortest recovery time was observed in propofol plus fentanyl group followed by midazolam plus fentanyl and Ketamine groups, as propofol has a favorable pharmacokinetic profile with a short half life and rapid elimination **(17)**.

Correia et al. (3) went in concordance with our results who concluded that sedation with propofol plus fentanyl leads to shorter recovery time than midazolam plus fentanyl group and this was confirmed by **Poulos et al. (20)** who reported that the use of propofol plus fentanyl resulted in less patient time in the endoscopy unit, quicker recovery and faster discharge than regimen using midazolam plus fentanyl**.**

Eloubeidi et al. (21) disagreed with our finding and reported that sedation with Ketamine had better quality and depth of sedation with shorter recovery time than sedation with midazolam alone, because they used Ketamine as adjunct to conscious sedation in patients who were difficult to sedate with midazolam alone, but in our study the addition of fentanyl to midazolam decreased midazolam dose with subsequent reduction in recovery time**.**

Finally, we can conclude that Sedation with propofol plus fentanyl for patients with liver cirrhosis undergoing UGIE was more safe, more efficacious with better comfort for patients as well as endoscopists and had shorter recovery time with early discharge than sedation either with midazolam plus fentanyl or with ketamine.

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