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Comparison of Fentanyl Citrate-midazolam-propofol and Fentanyl Citrate-ketamine Propofol Combinations with Regards to Efficiency and Safety in Sedation Practices for the ERCP

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MA and GA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors HK, UO, LK and AS managed the analyses of the study. Authors NK, GA and AS managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: The objective of our study is to compare the efficiency and safety of fentanyl citrate-midazolam-propofol combination with fentanyl citrate-ketamine-propofol combination used as sedative and analgesic medication in patients undergoing ERCP procedure.
Study Design: Randomized and prospective.
Place and Duration of Study: Department of Anaesthesiology and Reanimation (Gastroenterology Unit) between June 2009 and June 2010.
Methodology: 103 patients undergoing ERCP aged between 20-80 years, ASA I-III, participated in our study. Cases were randomly divided into two groups as group M(n=51) and group K(n=52). Fentanyl citrate 1 µg/kg IV was infused to all patients 5 minutes before the process.

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Group M: In addition to fentanyl, midazolam 0.04 mg/kg IV and propofol loading dose of 1mg/kg IV and maintenance dose of 4mg/kg/h IV were also infused.
Group K: In addition to fentanyl, ketamine 0.5mg/kg IV and propofol loading dose of 1mg/kg IV and maintenance dose of 4mg/kg/h IV were infused as well.
At the end of ERCP procedure, propofol infusion was terminated. The time required for the Richmond Alertness-Sedation Scale (RASS) score to reach -1 (recovery period) and its change from -1 to 0 in recovery room (discharge period) and also the development of side effects during the practice were recorded. After recovery period the patients were questioned if they felt pain during the procedure or not. If they felt any, the pain was evaluated according to Visual Analog Scale (VAS) score.
Results: Recovery period, discharge period and satisfaction of the endoscopist were similar between the two groups, however cardiovascular and respiratory system parameters were more stable in patients in Group K.
Conclusion: Our study pointed that fentanyl citrate-ketamine-propofol combination is probably preferable over fentanyl citrate-midazolam-propofol combination in terms of cardiovascular and respiratory stability during sedation in ERCP procedures.

Keywords: Sedation; ERCP; ketamine; midazolam.

1. INTRODUCTION

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a primary procedure that is used in the diagnosis and the treatment of gastrointestinal system (GIS) diseases and it is implemented as outpatient care. During the procedure, the patients lie in left lateral position. Throughout the procedure gag reflex is stimulated frequently causing fear, anxiety and vasovagal reactions aside from pain and distress. Additionally ERCP requires longer time than other upper GIS endoscopies [1]. The sedation is frequently needed to provide higher safety, success and comfort in such interventions [2-6].

Deep sedation is the recommended method for the patients undergoing ERCP procedure to keep them immobile during this process. While anaesthesia and sedation techniques provide comfort and safety to the patient, these should provide a fast recovery as well. The ideal agent to be given for this purpose should be quick and effective during the interference time and provide fast recovery, and it should also have minimal side effects [4]. Therefore, benzodiazepines, propofol, opioids or their combinations are preferable choices for this procedure) [1,3,4].

The objective of our study is to compare the efficacy and safety of the combinations of fentanyl citrate-midazolam-propofol with fentanyl citrate-ketamine-propofol, which are used for sedation, in patients undergoing ERCP.

2. MATERIALS AND METHODS

2.1 The Sample

A total of 48 women and 55 men, aged between 20-80 and ASA I-III planned to receive ERCP, participated in our study after receiving their written consent and local ethical committe's approval that accepts the principles of Helsinki Declaration. (Number of approval 547, date: 26.02.2009, the chairperson of the ethics committee Mehmet Celebisoy).

Pregnant women, chronic sedative opioid drug users, patients under 18 and above 80 years old, patients received general anaesthesia within last 7 days or on medication affecting the central nervous system, patients with adrenocortical insufficiency, psychiatric disorder and patients whose body mass index were under 18 and above 35 were not involved in the study.

2.2 Procedure

The randomized cases were divided into two groups. Electrocardiography (ECG), non-invasive blood pressure measurement, respiratory rate and pulse oximetry monitoring were implemented to all cases. Vascular access was established with 20G peripheral vein catheter and % 0,9NaCl was started to infuse. The basal measurement values; heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), peripheral oxygen saturation (SPO_2), respiratory rate (RR) and Richmond Alertness Sedation Scala (RASS) were documented before the procedure. Three lt/min oxygen was given to the patients through nasal cannula. All the ERCP procedures were performed on duodenoscopy table and in left lateral position.

Fentanyl citrate 1µg.kg^{-1} IV was infused to all patients, 5 minutes before the process.

In Group M: the procedure started after midazolam 0.04mg.kg^{-1} IV and propofol loading dose of 1mg.kg^{-1} IV and maintenance dose of 4mg.kg^{-1}.h^{-1} IV were infused in addition to fentanyl.

In Group K: the procedure started after ketamine 0.5mg.kg^{-1} IV and propofol loading dose of 1mg.kg^{-1} IV and maintenance dose of 4mg.kg^{-1}h^{-1} IV were infused in addition to fentanyl, and the intervention of duodenoscopy was allowed. The time passed till the duodenoscope ejection was documented and it was named as duodenoscopy time. A 0.3mg.kg^{-1} IV bolus of propofol was infused to both groups as additional dose in necessary conditions (e.g., mobility, cough).

The patients were tried to be kept in sedation level of RASS:-4 (Richmond Alertness-Sedation Scale -4: respiration is not depressed and eyes are open in response to physical stimulus) or RASS:-5 (Richmond Alertness-Sedation Scale -5: called evocable phase, in which respiration is not depressed and the patient could not respond to any stimulus).

The additional infused propofol doses were documented. During the process, HR, SAP, DAP, MAP, SPO_2, RR, side effects and RASS scores were documented. All the ERCP procedures were performed by the same experienced gastroenterologist.

Side effects developed during the process such as hypoventilation (<8 respiration/min), apnea (suspension of external breathing for 30 seconds), hypotension (MAP>30% decrease below basal levels), hypertension (MAP>30% increase above basal levels), arrhythmia, bradycardia (<50 pulse.min^{-1}), desaturation (SPO_2 reduction below 90%) were documented. Increasing oxygen flow to 10lt/min in case of SPO_2 reduction below 90%, infusion of Ephedrine 5-10mg IV in case of hypotension, infusion of Nitroglycerine 0.1-0.2mg i.v (1.5-3µg.kg^{-1}) in case of hypertension were planned and total dosages infused were documented.

In cases of hypoventilation and apnea, the O_2 flow was increased to 10lt.min^{-1} while performing patient's head extension and chin lift or jaw thrust in order to prevent an oxygen saturation reduction below 90%. After all, in case of no recovery, the procedure was

terminated and the patient was supported with bag-mask ventilation and was intubated when necessary. These cases were excluded from the study.

After the beginning of the propofol infusion, the ERCP intervention continued with measurements every 2 minutes in the first 10 minutes and then every 5 minutes until the end of the procedure. The total amount of ketamine, propofol, midazolam dosages infused during the ERCP process was documented. After the completion of the ERCP procedure, the time passed till RASS value rise to -1 (recovery period), rise from -1 to 0 in recovery room (discharge period) and the side effects developed during the procedure were documented. Besides, after recovery period all patients were questioned if they were conscious or felt any pain during the procedure. Afterwards, pain assessment was evaluated according to VAS. (Visual Analog Scale (VAS) ranging from 0cm (no pain) to 10cm (worst imaginable pain) is used widely for pain measurement). While the patient satisfaction was determined in this manner, patients' mobility, hiccoughs developed in the course of the procedure, the existence of intestinal mobility and the instability in hemodynamic parameters were evaluated and endoscopist satisfactory was also documented. The cases with 0 (zero) RASS value were given instructions and discharged.

2.3 Statistical Methods

Statistical Package for Social Sciences (SPSS) for Windows 17.0 program was used for the statistical analysis. Besides the descriptive statistical methods (mean, standard deviation, percent), Paired sample t statistical analyses was used in quantitative data comparison among the groups. For the qualitative data comparison between two groups, Independent sample t test was used. The results were evaluated as statistically significant in the level P<,05.

3. RESULTS

Total of 51 cases in Group M and 52 cases in Group K were participated in this randomized prospective study. In 2 cases in Group M, who were planned to receive ERCP procedure, duodenoscope was unable to pass through the lumen because of the intra abdominal bulk and obstructive jaundice, so that procedure could not be performed and these cases were excluded from the study.

Statistically significant difference was not determined between the groups, in terms of demographical features, age, body weight and gender (Table 1).

Table 1. The demographical features of the cases

	Group M (n=51) Mean±SD	**Group K (n=52) Mean±SD**	***P***
Age (year)	59.75±13.81	63.46±17.30	0.232
Body weight(kg)	61.69±10.53	67.77±16.15	0.255
Gender			
Male (n/%)	27(52.9)	28(53.8)	0.598
Female (n/%)	24(47.1)	24(46.2)	0.456
ASA			
1(n/%)	19(37.3)	22(42.3)	0.881
2 (n/%)	23(45.1)	20(38.5)	0.790
3 (n/%)	9(17.6)	10(19.2)	0.901

The distribution of the cases according to their diagnoses was shown in Table 2.

Table 2. The distribution of the cases according to the diagnoses

	Group M		Group K	
	n	%	n	%
Choledochus stone	38	74.50	36	69.2
Choledochus disorder	6	11.76	7	13.5
Pancreas head tm	5	9.80	6	11.5
Chronic pancreatitis	1	1.96	1	1.9
Postop bilier disorder	1	1.96	2	3.8

When comparing the intergroup MAP mean values, a statistically significant difference was not determined between two groups before and in the course of the procedure. However, after the procedure in Group K MAP at 20th min. was statistically significantly higher (P<,05) (Table 3).

Table 3. Distribution of the cases according to MAP (Mean Arterial Pressure)

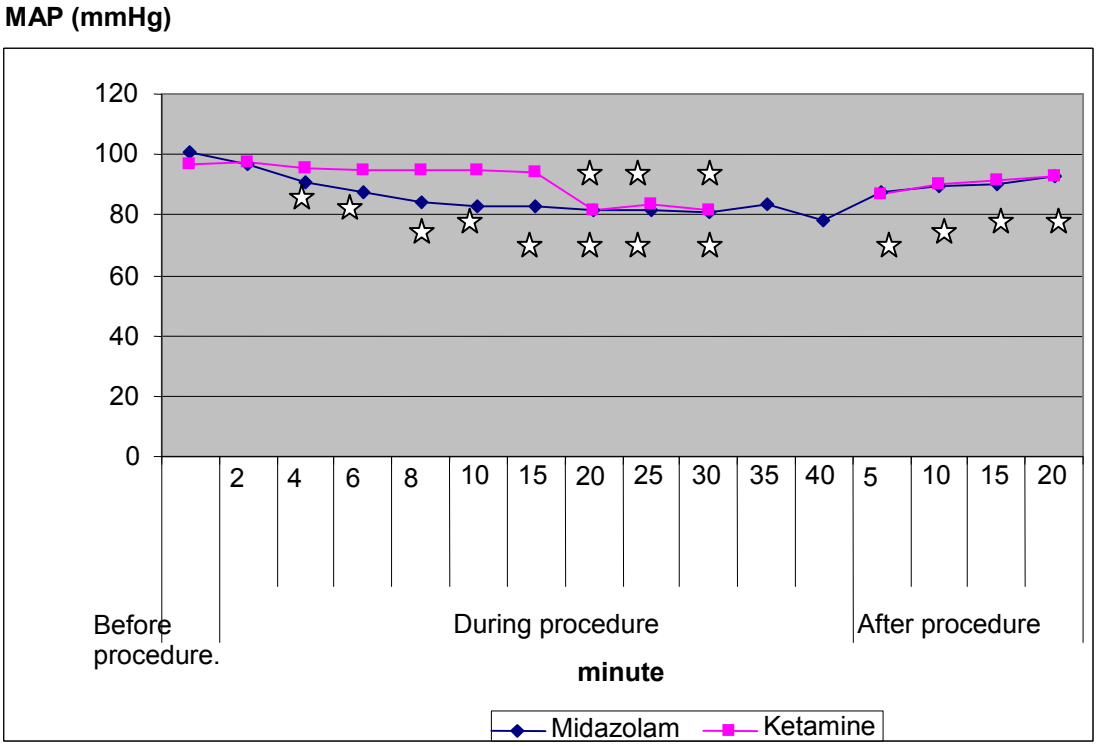
Time (dk.)	MAP (mm Hg)				*P*
	Group M (n=51)		Group K (n=52)		
	Mean	SD	Mean	SD	
0	101	16.67	96.77	12.20	0.139
2	97.08	10.17	97.40	10.53	0.257
4	91.04	9.77	95.52	10.08	0.653
6	87.45	9.23	94.87	8.94	0.378
8	84.45	9.10	94.56	7.79	0.259
10	82.57	8.71	95.87	8.05	0.093
15	82.91	9.22	94.12	9.02	0.262
20	81.45	8.63	81.73	8.55	0.909
25	81.83	6.24	83.62	11.92	0.737
30	81.00	6.68	81.50	6.36	0.935
35	83.50	13.00			
40	78.33	1.52			
Process Last 5 Min.	87.43	8.62	86.63	8.59	0.640
Process Last 10 Min.	89.43	9.12	90.20	8.46	0.380
Process Last 15 Min.	90.47	8.46	91.73	8.40	0.102
Process Last 20 Min.	92.80	8.14	93.86	8.77	0.004*

** Independent sample t test statistically significant in the level of P<,05*

The MAP mean values of the cases in Group M, in 4, 6, 8, 10, 15, 20, 25 and 30th minutes, were lower than basal value before the procedure, which was found statistically significant (*P*<,05). And in Group K, the MAP mean values were decreased in 20, 25 and 30th minutes compared with basal value which was found statistically significant. The MAP mean values of the cases in Group M, in 5, 10, 15 and 20th minutes in the period after the procedure, were lower than the basal value before the procedure, which was found statistically significant (*P*<,05). And as for the cases in Group K, there was no statistically significant difference when comparing the MAP mean value and the basal value in the periods after the procedure (Graphic 1).

When comparing the intergroup HR values, there was no statistically significant difference between the two groups before, after and in the course of the procedure (Table 4).

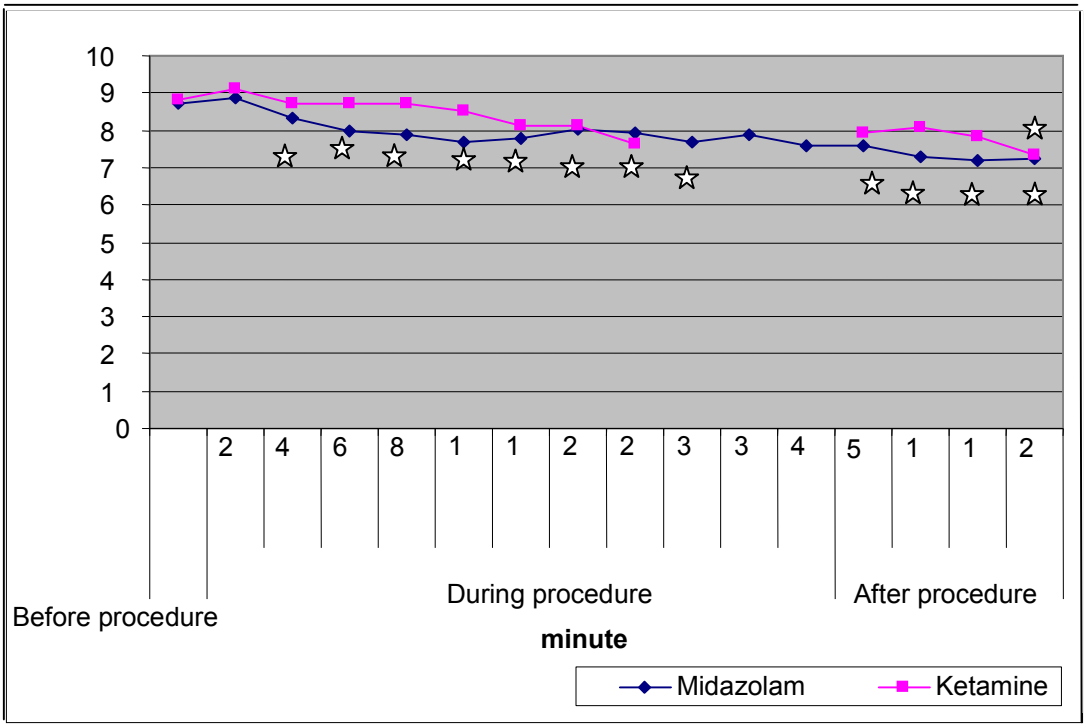
The HR mean values of the cases in Group M, in 4, 6, 8, 10, 15, 20 and 25th minutes, were lower than basal value before the procedure was found statistically significant (*P*<,05). And in the cases of Group K, when comparing the HR mean values with basal value before the procedure, a statistically significant difference was not found. The HR mean values of the cases in Group M, were decreased in 5, 10, 15 and 20th minutes in the period after the procedure compared with basal value before the procedure was found statistically significant. And as for the cases in Group K, the HR mean values were decreased in the 20th minute after the procedure compared with the basal value was found statistically significant (*P*<,05) (Graphic 2)



Graphic 1. MAP mean values of the groups in the periods before, during and after the procedure (mmHg)* P<,05

When comparing the intergroup SpO_2 values, a statistically significant difference was not determined between the two groups before, after and in the course of the procedure (Table 5).

The SpO_2 mean values of the cases in Group M, in 2, 4, 6, 8, 10, 15, 20, 25, 30 and 35th minutes, were higher than basal value before the procedure was found statistically significant (*P*<,05). And in the cases of Group K were increased compared with basal value only in the period after the procedure in 20, 25 and 30th minutes was found statistically significant (*P* <,05). The SpO_2 mean value of the cases both in Group M and Group K were increased in 5, 10, 15 and 20th minutes compared with basal value before the procedure was found statistically significant (*P*<,05) (Graphic 3).



Graphic 2. HR mean values of the groups in the periods before, during and after the procedure (pulse/min)* *P*<,05

Table 4. Heart rate (HR) values between groups (rate/min.)

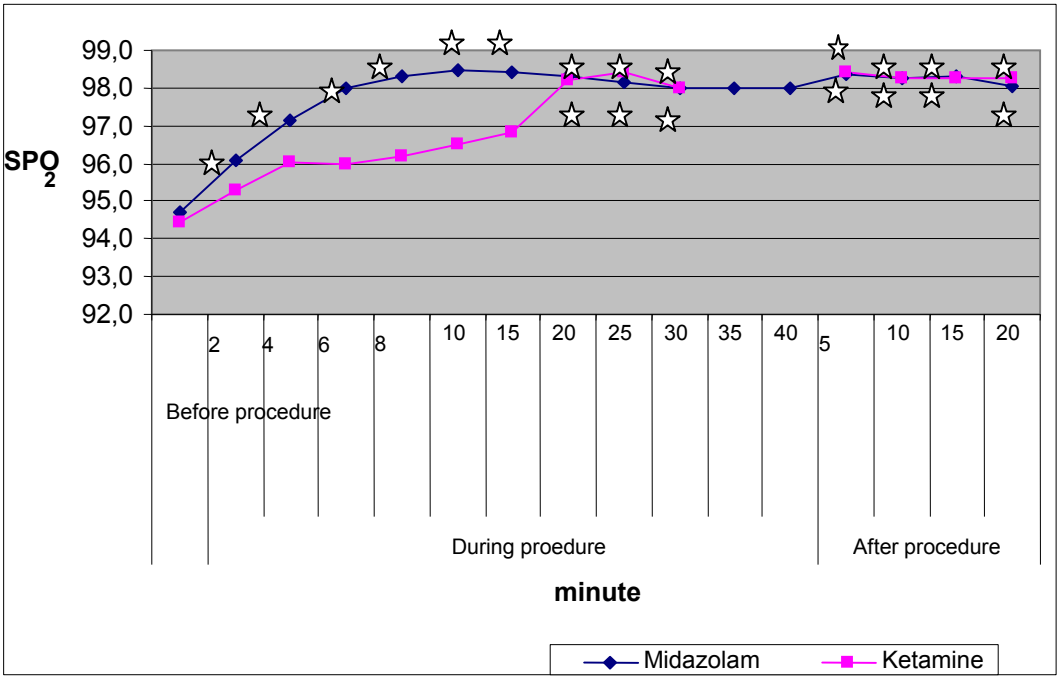
Time (dk.)	HR (Rate/Min.)				P
	Group M (n=51)		Group K (n=52)		
	Mean	SD	Mean	SD	
0	87.20	11.33	88.40	15.49	0.653
2	88.45	12.45	91.85	14.64	0.208
4	83.22	11.62	87.58	13.23	0.290
6	80.00	9.88	86.37	13.57	0.315
8	78.61	9.30	87.37	12.87	0.216
10	76.96	8.33	85.28	13.19	0.073
15	77.98	7.75	81.23	13.64	0.151
20	80.14	8.01	81.06	11.29	0.741
25	79.50	9.09	79.92	12.55	0.944
30	76.75	8.99	76.50	3.53	0.973
35	78.75	10.68			
40	76.00	11.53			
Process Last 5 Min.	75.69	8.23	79.17	10.99	0.072
Process Last 10 Min.	72.94	6.35	80.66	9.44	0.060
Process Last 15 Min.	71.73	5.85	78.98	8.46	0.119
Process Last 20 Min.	72.26	5.17	73.53	8.34	0.361

Independent sample t test

Table 5. SpO_2 mean values between groups

Time (dk.)	SpO_2				P
	Group M (n=51)		Group K (n=52)		
	Mean	SD	Mean	SD	
0	94.71	0.72	94.46	0.93	0.144
2	96.08	0.86	96.27	1.12	0.337
4	97.14	0.91	97.50	0.75	0.030
6	97.98	0.76	98.13	0.59	0.254
8	98.33	0.58	98.40	0.66	0.570
10	98.49	0.57	98.48	0.64	0.938
15	98.40	0.53	98.44	0.69	0.711
20	98.32	0.56	98.18	0.63	0.420
25	98.17	0.40	98.42	0.66	0.417
30	98.00	0.00	98.00	0.00	
35	98.00	0.00			
40	98.00	0.00			
Process Last 5 Min.	98.39	0.53	98.40	0.60	0.917
Process Last 10 Min.	98.24	0.42	98.27	0.56	0.732
Process Last 15 Min.	98.29	0.54	98.27	0.66	0.835
Process Last 20 Min.	98.06	0.24	98.27	0.53	0.11

Independent sample t test



Graphic 3. SPO_2 mean values of the groups in the periods before, during and after the procedure (%): * *P*<,05

When comparing the intergroup respiration rate (RR) mean values, a statistically significant difference was not determined between two groups in basal period and in the period after the procedure; and a statistically significant increase was determined in the course of the procedure, in the cases of Group K, compared with the cases of Group M in 2, 4, 6, 8 and 10th minutes (*P*<,05), (Table 6).

Table 6. The mean distribution of respiration rate in groups (frequency/min)

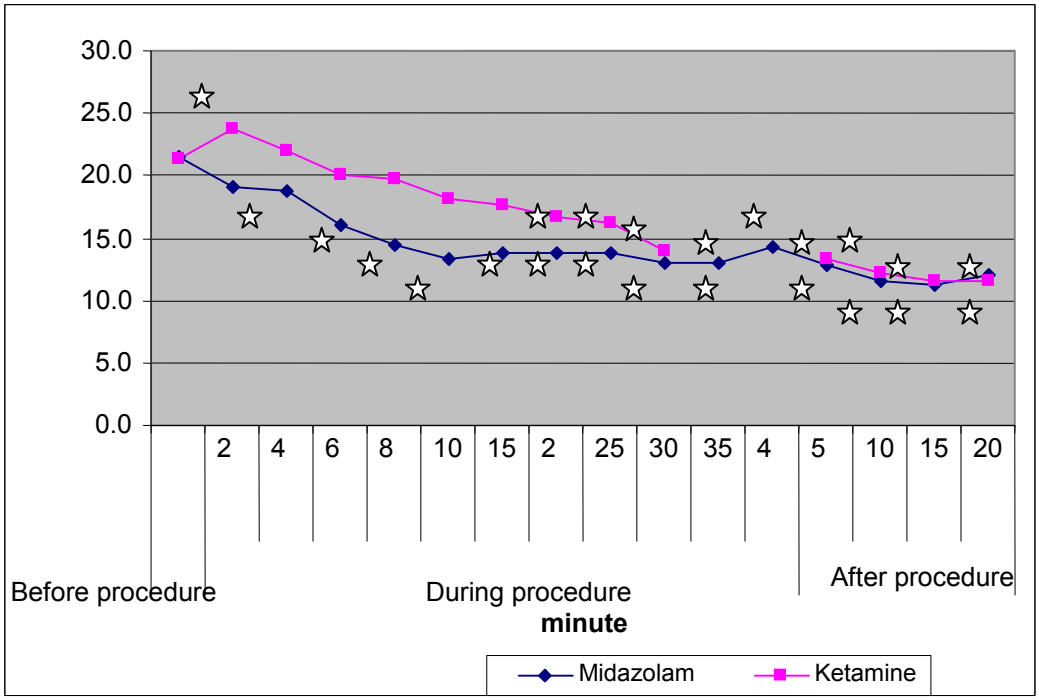
Time (dk.)	Respiration Rate				P
	Group M (n=51)		Group K (n=52)		
	Mean	SD	Mean	SD	
0	21.55	5.10	21.40	3.81	0.870
2	19.06	6.11	23.81	5.66	0.004*
4	18.76	4.47	22.00	4.76	0.003*
6	16.00	3.41	20.01	3.83	0.001*
8	14.45	2.63	19.79	3.68	0.000*
10	13.25	2.10	18.17	3.72	0.002*
15	13.72	2.56	17.60	3.40	0.157
20	13.86	3.38	16.76	3.47	0.349
25	13.83	2.13	16.16	2.79	1.000
30	13.00	2.44	14.00	1.41	0.633
35	13.00	2.44			
40	14.33	1.52			
Process Last 5 Min.	12.78	2.44	13.29	2.76	0.329
Process Last 10 Min.	11.63	1.72	12.12	1.78	0.161
Process Last 15 Min.	11.29	1.22	11.62	1.23	0.188
Process Last 20 Min.	11.96	1.26	11.55	1.11	0.086

** Independent sample t test statistically significant in the level of P <,05*

The respiration rate mean values of the cases in Group M, in 4, 6, 8, 10, 15, 20, 25, 30, 35 and 40th minutes, were higher than basal value before the procedure, which was found statistically significant (*P*<,05). And in the cases of Group K, the respiration rate mean values were increased in the 2nd minute compared with basal value, and decreased in 20, 25 and 30th minutes which was found statistically significant (*P*<,05). The respiration rate mean values of the cases in Group M were decreased in 5, 10, 15 and 20th minutes compared with basal value before the procedure was found statistically significant (*P*<,05). And in the cases of Group K, the respiration rate mean values were decreased in 5, 10, 15 and 20th minutes compared with basal value was found statistically significant (*P*<,05) (Graphic 4).

When comparing the duodenoscopy period, recovery period, and discharge period values, a statistically significant difference was not found (Table 7).

Patient to move and with hiccoughs in the course of the procedure, the existence of intestinal mobility and the constitution hemodynamic changes were evaluated and endoscopist satisfactory was determined. Although there is no statistically significant difference between the groups, the endoscopist satisfactory was determined as quite good in 92.3% and good in 7.7% of the cases of Group K; It was also determined as quite good in 90.1% and good in 9.9% of the cases of Group M. (Table 8).



Graphic 4. Respiratory rate mean values of the groups in the periods before, during and after the procedure (frequency/min):* *P*< ,05

Table 7. Procedure period, recovery period, discharge period

	Group M (n=51) Mean ± SD	**Group K (n=52) Mean±SD**	***P***
Procedure period	18.53±6.80	19.71±4.13	0.282
Recovery period (Time passed from RASD:-4 to RASD: -1) (min.)	4.14±0.66	3.91±0.80	0.330
Discharge period (Time passed from RASD: -1 to RASD: 0) (min.)	20.10±3.86	19.31±5.29	0.390

Table 8. Endoscopist satisfaction distribution

	Group M		**Group K**		***P***
	n	**%**	**n**	**%**	
Satisfaction					
Bad	-	-	-	-	
Mid	-	-	-	-	
Good	5	9.9	4	7.7	0.156
Excellent	46	90.1	48	92.3	0.149

Chi square test

As simultaneously evaluating all the adverse effects, were observed in the course of the procedure, a difference between the groups was not found (Table 9).

Table 9. Side effect distribution in cases according to groups (%)

Side effect	Group M (n=51) n /%	Group K (n=52) n /%	p
Patient awareness	-	-	-
Pain	-	-	-
Hypoventilation	7 (16.27)	3 (5.76)	0.075
Hypotension	-	-	-
Desaturation (requiring intervention)	-	-	-
Apnea	-	-	-

Chi- Square test

When these complications were evaluated separately the incidence of consciousness pain, bradycardia, hypotension and reduction in oxygen saturation developed during the procedure were almost similar in both groups. While hypoventilation was observed in 7 patients in Group M, this number was 3 in Group K. This hypoventilation developed 1 minute after the induction and the respiration rate decreased to 7-8 frequency.minute^{-1}. Without causing desaturation and apnea, hypoventilation recovered spontaneously within 30-35 seconds without requiring intervention.

As there was nota statistical difference in the total propofol dosages used for sedation in the course of the procedure; the additional dosages to provide sedation was required for 3 patients in Group M and 1 patient in Group K (Table 10).

Table 10. Medication dosages infused in course of the procedure (Mean±SD)

Propofol (mg)	Group M (n=51)	Group K (n=52)	p
Induction	64.92±10.90	65.96±9.06	0.600
Infusion	78.31±30.70	81.44±18.60	0.533
Additional dosage	20.70±2.79	15.00±0.00	0.083
Total	147.296±36.41	147.690±23.89	0.948

3. DISCUSSION

The appropriate sedation is needed during the ERCP intervention, for the procedure achievement [4,5]. So, providing the patient comfort and safety may also reduce incidence of the complications, besides easing gastroenterologist's intervention [4,6].

Midazolam provides a good sedation and perfect amnesia, but it may cause hypotension and respiratory depression. Besides, it does not have analgesic effect [7]. Only medication with propofol requires higher dosages than combination medication to provide appropriate conditions for the ERCP intervention and this causes cardiovascular and respiratory system depression and loss of defensive reflexes. Besides, the lack of its analgesic effect causes some restrictions to its usage alone. In the anaesthesia induction performed with propofol, it can be used in combination with ketamine in subanesthetic dosages [8-10]. So, as the pain relating to propofol could be prevented [9], a better analgesia can be provided comparing to

the propofol and fentanyl combination, better hemodynamic datum can be obtained and the respiratory depression can be prevented in postoperative period [10].

Ong et al. [11] only used propofol to Group A and sedoanalgesic cocktail (midazolam, ketamine, pentazocine) to Group B, totally to 198 patients undergoing ERCP, and made a comparison on the process tolerance of the patients according to VAS score and the complications developed Temporary desaturation rate was 4,8% in Group A and 15% in Group B. It was determined that the process tolerance of the cocktail group was better. In our study, while hypoventilation was diagnosed in 7 patients in Group M, this number was 3 in Group K. Accordingly, the hypoventilation and desaturation were together, but these recovered spontaneously without requiring intervention or disruption of process. It was shown that respiratory rate decreased to 7-8.min^{-1}. 30-40 seconds after the induction**,** this rate increased to its normal range after 20-25 seconds. In the meantime, the minimally measured saturation was 90%. We think that the reason of hypoventilation and desaturation to last a short time was the medication's being short acting by given in low and titrated dosage. Meanwhile, there was no difference in peripheral oxygen saturation values between the groups. Garewal et al. [12] searched a worldwide literature about ways of providing sedation for ERCP procedure involving a total of 510 participants and identified four randomized trials appropriate for review. They compared using of midazolam/meperidine combination for conscious sedation with using propofol for deep sedation in patients undergoing ERCP procedure. According to the results in patients receiving propofol sedation, recovery is faster and better than in patients receiving midazolam/ meperidine combination sedation. Sethi et al. [13] found similar results regarding to propofol with a total number of 969 patients in their meta-analysis. In another ERCP study, Jung et al. [2] applied medication with only propofol to a group among 80 patients, as they used midazolam to the other group and monitored the blood pressure, pulsation, oxygen saturation and recovery times. MAPs decreased in both groups .This decrease was determined as 17% in the group medicated with only propofol, while it was 14% in group medicated with midazolam. In this study, because the recovery period and the discharge period was shorter with propofol than midazolam, it was determined that propofol was a better choice. In our study, comparing the intergroup MAP mean values, a statistically significant difference was not determined between two groups before and in the course of the procedure. However, the value of 20 min. in Group K, in the period after the procedure, was found significantly higher (P<,05). As analysing the groups within themselves, while a statistically significant decrease was not determined in the first 20 minutes comparing to the basal period in the cases of Group K, the MAP was low starting from the 4th minute in Group M during the first 30 minutes. We think that this difference is due to the positive inotropic effect of ketamine, observed in the first 20 minutes.

In their study, Ugur et al. [9] researched the effects of ketamine, infused with subanesthetic dosages before the propofol induction, on the pain and side effects that may develop in cardiovascular system depending upon the propofol. Whereas only propofol was infused to Group P, 0,5 mg.kg^{-1} after ketamine was infused to Group Ketamine/propofol. The oxygen saturations were measured higher than they were before the induction in both groups. And the MAP and HR changes were similar in both groups. While the difference was not statistically significant in the hemodynamic aspect, they determined the MAP decrease as 7,4% in the second minute in Ketamine/propofol group and 12% in the group that propofol was used singly. The MAP decrease in the tenth minute was determined as 7,2% in the ketamine/propofol group and 10,7% in the propofol group. The MAP and HR measurements in our study are similar to this study.

Seifert et al. [14] used singly propofol for a group (Group A) and midazolam/propofol combination for the other group (Group B) in 239 patients undergoing ERCP and endoscopy. A decrease of 17% in SAP and 10% in DAP in Group A, while a decrease of 15% in SAP and 9% in DAP in Group B was determined. The sedation efficiency was found similar in both groups. The exact recovery periods were 19±7 minutes in Group A and 25±8 minutes in Group B and this difference was found statistically significant. In our study, the time for recovery was in 4,14±0,66 minutes and the time for discharge was in 20±10 minutes in Group M, the time for recovery was in 3,91±0,80 and the time for discharge was in 19±5,29 minutes in Group K. The time for recovery was longer and the dicreases in SAP and DAP were more compared with the study of Seifert et al. The reason of this differance is the quantities of propofol and midazolam were higher in the study of Seifert et al than our study.

The HR mean values of the cases in Group M, in 4, 6, 8, 10, 15, 20 and 25th minutes, were lower than the basal value before the procedure (P<,05). Midazolam does not have any clear effect on heart rate. However, in our study, when it was used together with propofol infusion, significant negative inotropic and chronotropic effects came up compared with the beginning. In the cases of Group K, the HR mean value decreased in the 20th minute after the procedure compared with the basal value which was statistically significant. The reason of this decrease is the absence of the inotropic effect of ketamine.

When the intergroup RR mean values were compared, a statistically significant difference was not determined between the two groups in the periods before and after the procedure. It was determined that the RR mean values in 2, 4, 6, 8 and 10th minutes were significantly higher in the cases of Group K compared with the cases of Group M. When we analyse the groups within themselves, the respiration rate showed a significant increase in 2nd minute in Group K. This probably coincided with the ketamine peakin the circulation. In 2mg.kg^{-1} of induction dosage, ketamine may cause a temporary decrease in the minute ventilation, and it does not cause respiratory depression with its low dosages [7]. However, there are also different declarations. It was reported that the low dose of ketamine combined with fentanyl reduces the decrease in alveolar ventilation and minute volume [15]. Besides, it was also reported that the ketamine infusion stimulates ventilation [16]. The positive effect that we determined in RR, may be originated from ketamine's effect of reducing the decrease in the alveolar ventilation and the minute volume in subanesthetic doses [15] and also reducing the depression effect of propofol on the respiratory system [1]. Because its effect diminishes after 20, 25th minutes and besides, due to the sedative effect of propofol continued, the respiration rate may decrease later. Although we observed a significant decrease in the RR in Group M, it was seen that there is not any decrease in oxygen saturation.

In upper GIS endoscopy sedation study of the paediatric cases performed on 90 patients, Tosun Z. et al. [17] used propofol/fentanyl to one group and propofol/ketamine to the other group and they determined that the HR and RR after the induction was significantly lower in the propofol/fentanyl group compared with the propofol/ketamine group. This result supports our study and shows that despite the detractive effect of propofol on HR and RR, it is balanced with ketamine and a stable result is obtained from the hemodynamic aspect. It was shown that propofol and ketamine combination provide a better cardiovascular stability and the cardio depression effect of propofolis balanced with sympathomimetic effect of ketamine [1]. The positive effects of subanesthetic doses of ketamine infusion (lack of RR decrease and desaturation) in respiratory system before the induction with propofol in Group K were also shown in our study. These results about the effects of ketamine on the respiratory system are similar with the study by Morel et al. [16] Additionally Mildh et al. [15] reported

that ketamine prevents the reduction in minute volume and alveolar ventilation induced by fentanyl, but it doesn't prevent the reduction in oxygen saturation. And they associated this with the changes in oxygen consumption.

In our study, when we analysed the times for discharge no difference was found between the groups statistically. In another study, Whermann et al. [18] compared two groups of patients undergoing ERCP. They infused midazolam to one group and propofol to the other group and evaluated changes in vital signs, the time for recovery and the tolerance of the process. As a result, they decided that propofol was more effective, due to its quick action time, shorter recovery time and better cooperation of patients as well as similar tolerance for the process. In this study, Aldrete score of the patients became 9 in 29±8 minutes in midazolam group, and in 19±8 minutes in propofol group. The total midazolamdose is 7,8±3,1mg and propofoldose is 388±212mg. In our study, as cases in Group M were discharged in 20±10 minutes, the cases in Group K were discharged in 19±5,29 minutes and there was not a statistically significant difference between two groups. We think that the reason of shorter discharge period in our study originated from lesser dosage of propofol infusion.

In another study Varadarajulu et al. [19] studied on the efficiency and safety of ketamine in the endoscopic procedures in highly sedatized patients. They divided 175 patients into two groups and infused meperidin 50mg, midazolam 5mg; diazepam 5mg. Ketamin 20mg was infused in every 5 minutes in Group A, and 25 mg meperidin and 2,5 mg diazepam was infused in Group B, for providing the sedation depth. The sedation depth and endoscopist's satisfaction were higher and the recovery time was shorter in the ketamine group. In our study, patient mobility, hiccoughs developed in the course of the procedure, the existence of intestinal mobility and the constitution of hemodynamic changes, endoscopist's satisfaction were evaluated. A statistically significant difference was not determined between the groups (Table 8).

4. CONCLUSION

Today, the anaesthetists use benzodiazepine, opioid and propofol in sedation and analgesia practices in the procedures of ERCP, implemented as outpatient care. Even if any difference was not found between Group K and Group M with regards to recovery period, discharge period, endoscopist's satisfaction, it is shown that cardiovascular and respiratory system parameters were more stable in group K.

Therefore, we were of the opinion that the fentanyl-ketamine-propofol combination could be preferred to fentanyl-midazolam-propofol combination in sedation practices in ERCP procedures with regards of efficiency and safety.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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