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Effects of midazolam or tramadol premedication on early cognitive function in endoscopic retrograde cholangiopancreatography (ERCP): A randomized, controlled, double-blind study

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Abstract

Objective: To evaluate the sedative efficacy and effects on early period cognitive function of premedication in endoscopic retrograde cholangiopancreatography (ERCP).

Methods: Forty patients (18–70 years; American Society of Anesthesiology risk category I–III) undergoing elective ERCP were randomized to receive oral premedication with 0.15 mg/kg midazolam or 1 mg/kg tramadol. Cognitive function was determined by mini-mental test (MMT). Target scores for effective sedation were determined as a Bispectral index score of 70–90 and modified Ramsay Sedation Scale score (mRSS) of 2–4.

Results: Global MMT score was not significantly different between treatment groups at 60 min post-ERCP. A significant deterioration in the MMT subcategory of recall was determined in with midazolam versus tramadol. Level of sedation (mRSS) was higher in with midazolam compared with tramadol reaching statistical significance at 30 min after drug administration.

Conclusıons: Although more effective sedation was obtained with midazolam in patients undergoing ERCP, there was a dysfunction in memory recall. It was concluded, however, that early cognitive functions were generally preserved with both drugs.

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Introduction

Endoscopic interventions for diagnosis and treatment constitute a significant part of outpatient anaesthesia.[1] Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive endoscopic technique used for the diagnosis and treatment of biliary tract and pancreatic duct pathologies.[2] Because ERCP is a longer and more complex procedure than upper endoscopy and colonoscopy, deeper sedation and analgesia are required.[3] Trouble-free procedure time, early recovery and protection of cognitive function are essential in ERCP. Short-term and temporary postoperative cognitive dysfunction (POCD) may occur although POCD may also continue beyond 7 days.[5,6]

Moderate levels of sedoanalgesia may improve patient satisfaction and procedural comfort and can be achieved through premedication. The ideal premedication agent should provide sedation and anxiolysis, and should increase the quality of recovery and maintenance.[4] Midazolam and tramadol are short-acting drugs that may be used as premedication. Data regarding oral administration of tramadol in ERCP premedication have not been published in English. Furthermore, studies evaluating the effect of premedication on cognitive function in the early period after outpatient ERCP are also lacking.

The current study aimed to determine the sedative and analgesic contributions of premedication with oral midazolam or tramadol and the effects on early period cognitive function in patients undergoing elective ERCP under controlled remifentanil anaesthesia.

Patients and methods

Study population [B-heading]

Outpatients aged 18–70 years undergoing elective ERCP in the Endoscopy Unit of the Gastroenterology Department, Karadeniz Technical University Medical Facility, Trabzon, Turkey between September 2008 and January 2010 who were classified as having American Society of Anesthesiology (ASA) risk status I–III were enrolled in the current study. Patients were excluded if they were classified as having an ASA status of $>$ III, morbid obesity, major organ dysfunction (respiratory, renal and hepatic), history of drug addiction, known hypersensitivity for tramadol, midazolam or remifentanil, or a mini-mental test (MMT) score ≤ 23.

The study was registered with the Clinical Trials.gov protocol registration system (NCT02436980) and was approved by the Institutional Ethics Committee of Karadeniz Technical University (07.07.2008/No:499). All patients participating in the study provided written informed consent.

Study procedures [B-heading]

At 45 min prior to the start of the ECRP procedure, patients were taken to the preoperative preparation room of the Endoscopy Department. Vital signs including blood pressure, heart rate, peripheral oxygen saturation and respiration rate (Dash 2000 Patient Monitor, GE Medical Systems, Milwaukee, WI, USA), Bispectral index (BIS; BIS-XP Quatre, Aspect™ Medical Systems, St Newton, MA, USA), modified Ramsey Sedation Scale (mRSS)

score and pain score (numeric rating scale (NRS), 0–10) were recorded at baseline in all patients by the same researcher (HU) who was unaware of the study drug. Target scores for effective sedation were defined as: BIS of 70–90 and mRSS score of 2–4. Patients were randomized by closed-envelope method to receive 0.15 mg/kg midazolam (Dormicum®, Roche Müstahzarları A.Ş, Istanbul, Turkey) (group M) or 1 mg/kg tramadol (Contramal®, Abdi Ibrahim Ilaç San., Istanbul, Turkey) (group T) administered orally in 10 ml of cherry juice without particles.

Patients were moved to the endoscopy unit 30 min after administration of premedication. Nasal cannula were inserted to be maintained throughout the whole procedure and started with 4 l/dk O_2. With patients in the lateral decubitus position, analgesia and sedation at adequate depth was achieved during ERCP using 1 μg/kg remifentanil (Ultiva® GlaxoSmithKline, Istanbul, Turkey) administered intravenously via perfusor (Perfusor® compact S, B/BRAUN, Melsungen, Germany) for 5 min. Remifentanil was maintained at 0.2 μg/kg per min throughout the procedure. Incomplete sedation was considered when uncontrolled movements, hypertension (increase of ≥ 40 mmHg from baseline systolic blood pressure (SBP)), tachycardia (increase of ≥ 30% from baseline heart rate or ≥ 90 beats per min), BIS ≥ 90, or mRSS score ≤ 2 were observed. In cases of incomplete sedation, up to two further doses of 1 mg midazolam were administered intravenously. If, despite additional midazolam, sedation was still inadequate (mRSS ≤ 2 or BIS ≥ 90), 0.5 mg/kg propofol was administered intravenously as a rescue sedative. Over sedation was defined as hypotension (20% decrease from baseline in SBP or SBP < 90 mmHg), bradycardia (heart rate-≤ 50 beats per min), development of bradypnea (respiration rate ≤ six per min), oxygen desaturation ($SpO_2 \leq 90\%$), BIS ≤ 70, or mRSS score ≥ 5. In the event of over sedation, remifentanil infusion was temporarily discontinued. Anaesthesia management was carried out in all ERCP procedures by the same anaesthetist (IC) who was unaware of the premedication drug. ERCP procedures were performed by the same endoscopist (MA) who was also blinded to premedication drug. During the process, hyoscine-N-butyl bromide (Buscopan® 20 mg/ml ampoule, Eczacibasi Drug Company, Istanbul, Turkey), a smooth muscale anti-spasmolytic, was used to control oddi sphincter spasm; the amount of hyoscine N-butylbromide used was recorded.

Patients with a NRS score > 3 after entry to the recovery room post-ECRP received 1 g paracetamol intravenous infusion (Perfalgan®, Bristol-Myers Squibb, Istanbul, Turkey). Aldrete scores were recorded at entry to the recovery unit and after 60 min. Patients in whom ERCP was successfully completed or who had undergone their final study evaluations (in the case of an unsuccessful procedure), who did not experience any side effects, had a NRS score < 3 and who fulfilled recovery criteria (modified Aldrete sedation score ≥ 9), were discharged accompanied by a responsible adult attendant.

The primary study endpoint was measurement of early period cognitive function; the secondary endpoint was determination of sedative efficacy.

Patient evaluations [B-heading]

Vital signs were automatically measured at prespecified time-points during ERCP and in the recovery unit as shown Table 1. Sedation, agitation and pain levels were evaluated in terms of BIS, mRSS and NRS at various time-points before, during and after the procedure as presented in Table 1.

Table 1. Time-points for evaluation of vital signs, and sedation, agitation and pain using the Bispectral Index (BIS), modified Ramsey Sedation Scale (mRSS) score and numeric rating scale, respectively, in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) after premedication for sedoanalgesia.

	Time-point
T_1	Before premedication
T_2	30 min after premedication
T_3	1 min after ERCP induction[a]
T_4	3 min after ERCP induction[a]
T_5	5 min after ERCP induction
T_6	10 min after ERCP induction
T_7	15 min after ERCP induction
T_8	30 min after ERCP induction[a]
T_9	Entry to recovery unit after ERCP
T_{10}	Recovery unit 60 min post-ERCP

[a]Note, mRSS and BIS were not recorded at this time-points.

Cognitive function was evaluated before administration of premedication and 60 min post-ERCP using the MMT.[7] The MMT is an 11-question measure that tests five areas of cognitive function: orientation (10 points), registration memory (three points), attention and calculation (five points), recall (three points) and language (nine points) for a maximum score of 30 points. If MMT was ≤ 23 at 60 min post-ERCP, patients were considered to be cognitively impaired; a decrease of ≥ 2 in the total MMT score was considered as a decrease in cognitive function.[5–7]

Adequacy of patient sedation during ECRP was evaluated using an endoscopist-structured questionnaire administered after completion of the procedure. Endoscopist satisfaction with adequacy of sedation was scored as: 0 = bad, 1 = medium, 2 = good and 3 = excellent. Patient satisfaction score with sedation adequacy was also recorded before discharge as: 0 = bad, 1 = medium, 2 = good and 3 = excellent. Simple questionnaires were used to gauge patient experience of endoscopy and endoscopist satisfaction before discharge. Although unvalidated, both questionnaires were considered adequate for this pilot study.

Total remifentanil dose used during ERCP, need for additional analgesics (use of paracetamol in patients with a NRS score > 3), procedure success ratio (successful: unsuccessful procedures), side effects of treatment and patient preference for premedication during next ERCP were also recorded.

Statistical analyses

All statistical analyses were performed using SPSS® software, version 13.0.1 (SPSS Inc., Chicago, IL, USA). Variables were analysed using the Kolmogorov-Smirnov test to determine if they were normally distributed. Measurable data were compared between treatment groups using Student's *t*- test for normally distributed data and Mann–Whitney *U*-test for data not conforming to a normal distribution. Differences between groups over time were evaluated using repeat measures variance analysis (post-hoc paired *t*-test) for normally distributed data and Freidman's test (post-hoc Wilcoxon signed-rank test) for non-normally distributed data. χ^2-test was used to compare qualitative (nominal) and sequential (ordinal) data in the different groups. Measurable data were presented as mean ± SD and qualitative and sequential data as frequencies and percentages. The correlation between BIS and mRSS did not conform to a normal distribution and so was evaluated using Spearman's correlation analysis. A *P*-value of < 0.05 was considered to be statistically significant.

Sample size was calculated to be 23 patients per treatment group ($\alpha = 0.05$ and 95% confidence interval with accuracy estimate of d = 0.1 and $P = 0.5$). SPSS® software, version 13.0.1 (SPSS Inc., Chicago, IL, USA; Serial Number: 9069728) was used for

calculation of sample size. Withdrawal of patients from the study after randomization resulted in 20 patients in each treatment group being available for analysis in the per-protocol (PP) population. As a consequence, a post-hoc power analysis was performed on 20 patients per group. Sample size was based on the intra-group periodic examination; effect size was calculated as 1.50 according to mRSS difference between pre- and post-drug administration in group M and power was calculated as 0.99. In group T; effect size was calculated as 1.27 and power as 0.99. For the intra-group periodic examination, effect size was calculated as 1.01 according to the difference in BIS pre- and post-drug group M and power was calculated as 0.99. Effect size was calculated as 0.82 according to MMT test difference in group M and group T and power was calculated as 0.

Results

Of 54 patients scheduled for elective ERCP, 45 were recruited into the study and randomized to receive midazolam (group M, $n = 23$) or tramadol (group T, $n = 22$). Three patients were withdrawn from the study in group M and two were withdrawn in group T leaving 20 patients in each group in the PP population (Figure 1). Of the patients that were withdrawn, one patient in each treatment group experienced an unsuccessful ERCP procedure due to oddi sphincter spasm. The ERCP procedure under sedoanalgesia with premedication was completed with success and without complications in all patients included in the PP population. No significant between-group differences were observed with respect to demographics, ERCP characteristics or MMT markers in both the intention-to-treat (ITT) and PP populations (Table 2).

Mean arterial pressure was significantly lower in patients treated with midazolam premedication compared with patients who received tramadol at periods T_2–T_6 and T_{10} ($P = 0.039$, $P = 0.028$, $P = 0.034$, $P = 0.008$, $P = 0.017$ and $P = 0.007$, respectively) (Figure 2A). Decreases in MAP continued in normal physiological margins from pre-medication to discharge in both treatment groups. No statistically significant differences were observed between the two pre-medication groups in terms of heart rate or peripheral oxygen saturation (Figure 2B and Figure 2C).

Level of sedation, as measured by the mRSS, was higher in group M compared with group T and this reached statistical significance at 30 min after administration of premedication ($P = 0.013$) (Figure 3A). Compared with levels of sedation before premedication, mRSS scores were significantly higher at time-periods T_2, T_5, T_7, T_9 and T_{10} in patients receiving midazolam and at periods T_5, T_7 and T_9 in patients receiving tramadol respectively ($P = 0.0005$ both groups). No significant difference was found between treatment groups at periods T_1–T_{10} with respect to BIS values (Figure 3A). A significant decrease in BIS scores was determined between baseline (T_1) and time-periods T_2–T_9 and T_5–T_9 in group M and group T, respectively ($P = 0.0005$ both groups). There was no significant between-group differences in the rate of patients reaching target sedation levels (mRSS score, 2–4; BIS,70–90) after premedication (group M, 25%; group T, 0%). A significant negative correlation between BIS and mRSS score was observed at time-points T_5 and T_7 (5 min and 15 min after premedication) and at T_9 (entry to the recovery room) ($P \leq 0.025$; Table 3). BIS and mRSS scores were more strongly correlated in group M compared with group T.

There was no difference between pre-medication treatment groups with regards to MMT global score at baseline (T_1) or at 60 min after ERCP (T_{10}). Similarly, there were no significant differences between treatment groups at T_1 or T_{10} in the MMT subcategories of orientation, registration,

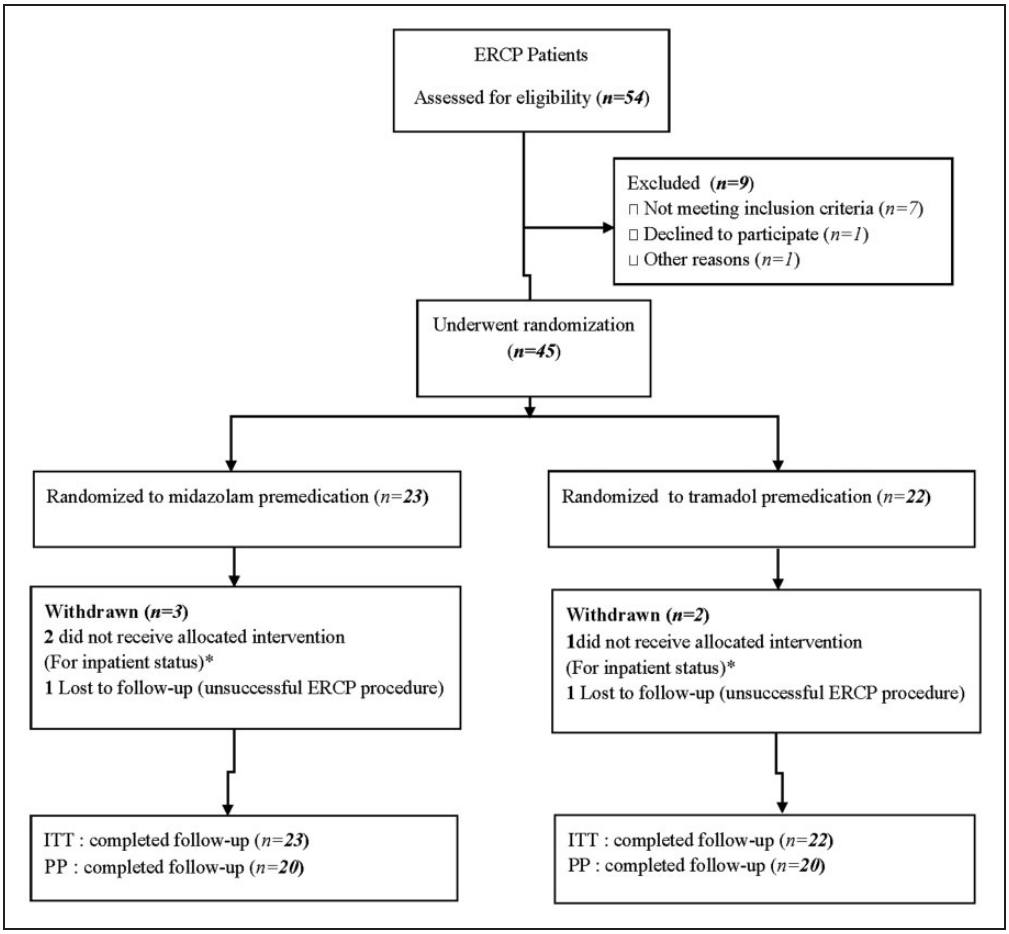

Figure 1. CONSORT flowchart of patients enrolled in a study investigating the effects of premedication with midazolam or tramadol on early cognitive function in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). *Patients can not be discharged from hospital after ERCP procedure. ITT: intention-to-treat; PP: per protocol.

attention and calculation or language (Figure 4). A significant deterioration in the recall subcategory was determined in the midazolam group but not in the tramadol group ($P = 0.024$; Figure 4). A decrease in total MMT score and all subcategories was determined in the midazolam group at 60 min post-ERCP with respect to baseline, but this did not reach statistical significance. Although there was a decrease in MMT total score in the tramadol group, no decrease was observed in 'memory' (recall) subcategory.

Pain levels, as determined by NRS scores, and need for additional analgesic medication were not significantly different between groups at any time-point during the study (data not shown). Similarly, no differences were observed between premedication groups with regards to total remifentanil infusion during ERCP and requirement for additional bolus midazolam (data not shown).

Table 2. Demography, endoscopic retrograde cholangiopancreatography (ERCP) characteristics and mini-mental test (MMT) markers in patients undergoing ERCP after premedication with midazolam (group M) or tramadol (group T).

	Intention-to-treat ($n = 45$)		Per-protocol ($n = 40$)	
	Group M ($n = 23$)	Group T ($n = 22$)	Group M ($n = 20$)	Group T ($n = 20$)
Age, years	53.21 ± 10.80	48.19 ± 12.65	52.45 ± 12.70	47.25 ± 13.49
Gender				
Male	9 (39.1)	12 (54.5)	7 (35.0)	11 (55.0)
Female	14 (60.9)	10 (45.5)	13 (65.0)	9 (45.0)
Weight, kg	73.18 ± 14.4	72.69 ± 14.1	72.05 ± 16.10	73.75 ± 13.83
ASA Class				
I	8 (34.8)	11 (50.0)	6 (30.0)	11 (55.0)
II	14 (60.9)	8 (36.4)	14 (70.0)	7 (35.0)
III	1 (4.3)	3 (13.6)	0	2 (10.0)
ERCP indication				
Pancreatitis	6 (26)	4 (18)	4 (20)	3 (15)
Cholangitis	5 (22)	7 (32)	5 (25)	7 (35)
CBD stone	12 (52)	11 (50)	11 (55)	10 (50)
ERCP procedure time, min	40.69 ± 16.60[a]	37.70 ± 9.16[a]	36.15 ± 14.64	31.40 ± 3.95
Hyoscine-N-butylbromide, mg/kg	8.65 ± 3.21[a]	10.27 ± 4.21[a]	7.22 ± 2.14	9.22 ± 3.65
Educational status score[b]				
0	7 (30.4)	2 (9.1)	7 (35.0)	2 (10.0)
1	0	3 (13.6)	0	3 (15.0)
2	6 (26.1)	10 (45.6)	5 (25.0)	9 (45.0)
3	4 (17.4)	1 (4.5)	2 (10.0)	0
4	4 (17.4)	2 (9.1)	4 (20.0)	2 (10.0)
5	2 (8.7)	4 (18.1)	2 (10.0)	4 (20.0)
Duration of education, years	6.1 ± 4.34	6.9 ± 5.45	5.6 ± 5.24	6.75 ± 5.61

Data presented as mean ± SD or *n* (%) patients.

No statistically significant between-group differences; $P \geq 0.05$ (student's *t*- test or Mann–Whitney *U*-test).

[a]Procedure time and dose of hyoscine-N-butylbromide in group M determined in 21 patients.

[b]Educational status score: 0 = illiterate, 1 = literate, 2 = primary school, 3 = secondary school, 4 = high school, 5 = university).

ASA: American Society of Anesthesiology; CBD: common bile duct.

No difference in parasympathetic need was observed between patients who received midazolam or tramadol premedication (Table 2.).

Patient satisfaction and endoscopist satisfaction scores with sedation were not significantly different between patients in group M and group T (Table 4). Side effects of treatment occurred at similar rates in both treatment groups, with the exception of hypertension, which was experienced by significantly more patients in group T compared with group M ($P = 0.044$; Table 4).

Discussion

The current study demonstrated that premedication with oral midazolam prior to ERCP was associated with a greater sedative action compared with tramadol premedication. Cognitive function in the early period

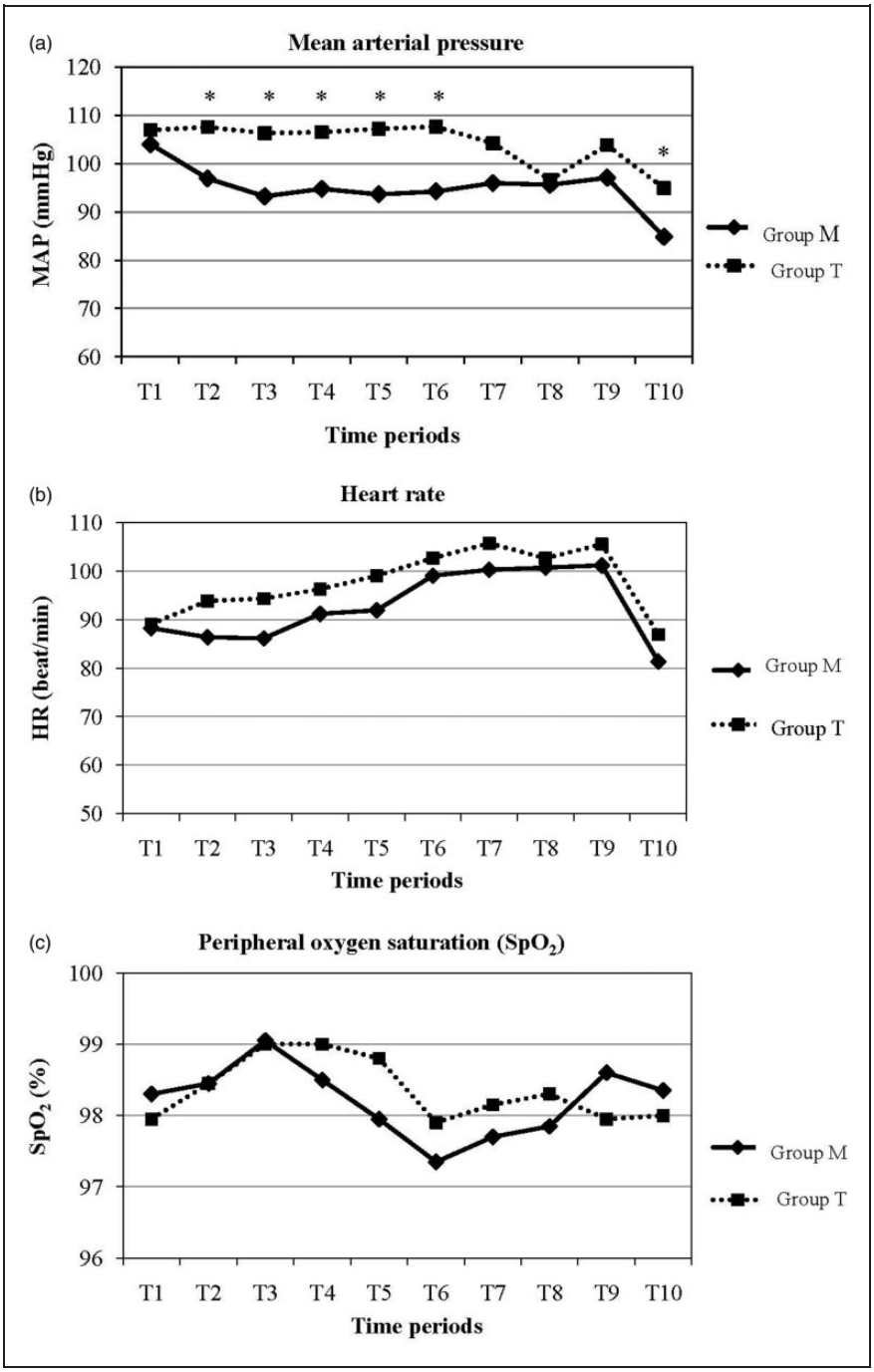

Figure 2. Vital signs over time in patients who received premedication with 0.15 mg/kg midazolam orally (group M, $n = 20$) or 1 mg/kg tramadol orally (group T, $n = 20$) prior to undergoing endoscopic retrograde cholangiopancreatography (ERCP). (a) mean arterial pressure (MAP), (b) mean heart rate (HR), (c) mean peripheral oxygen saturation (SpO2). Time (T) periods are as noted in Table 1. *$P > 0.05$ (variance analysis (post-hoc paired *t*-test)).

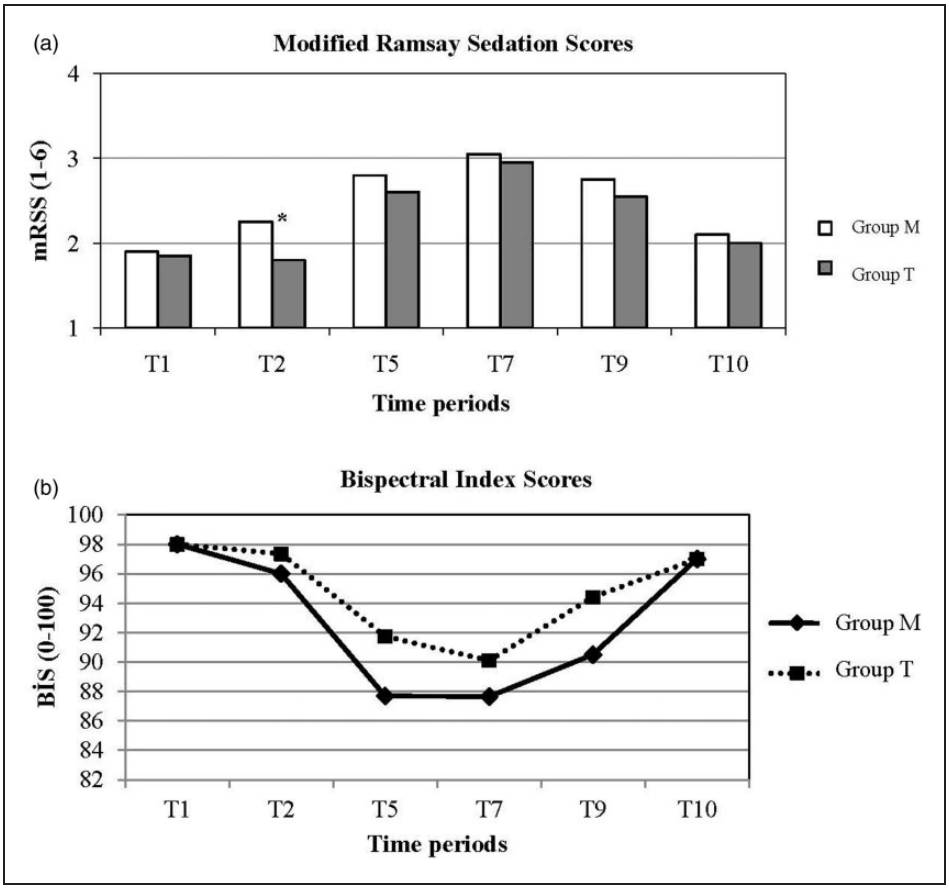

Figure 3. Sedation and depth of anaesthesia in patients who received premedication with 0.15 mg/kg midazolam orally (group M, $n = 20$) or 1 mg/kg tramadol orally (group T, $n = 20$) prior to undergoing endoscopic retrograde cholangiopancreatography (ERCP). Time (T) periods are as noted in Table 1. (a) Modified Ramsay Sedation Scale scores (mRSS); data presented as median. mRSS scores were significantly higher at time-periods T_2, T_5, T_7, T_9 and T_{10} in patients receiving midazolam and at periods T_5, T_7 and T_9 in patients receiving tramadol respectively ($P = 0.0005$ both groups; χ^2-test) *$P = 0.013$ (χ^2-test). (b) Bispectral Index scores (BIS); data are presented as mean. A significant decrease in BIS scores was determined between baseline (T_1) and time-periods T_2–T_9 and T_5–T_9 in group M and group T, respectively ($P = 0.0005$ both groups; variance analysis (post-hoc paired *t*-test)).

following ERCP was preserved with both midazolam and tramadol although some memory impairment was observed in patients who received midazolam prior to the procedure.

There is, as yet, no consensus in the medical literature regarding the safest and most effective doses of sedative agents during ERCP. Remifentanil is an opioid that can be used alone or with other sedative agents in endoscopic gastrointestinal procedures and other outpatient interventions.[8–11] It has previously been demonstrated that adequate and safe sedoanalgesia can be obtained with midazolam premedication and remifentanil

Table 3. Correlation between Modified Ramsay Sedation Scale score (mRSS) and Bispectral index (BIS) in patients who received premedication with midazolam (group M) or tramadol (group T) prior to undergoing endoscopic retrograde cholangiopancreatography (ERCP).

	Group M ($n = 20$)		Group T ($n = 20$)	
Time-periods	*r*	Statistical significance	*r*	Statistical significance
T_1 (before premedication)	−0.076	NS	−0.096	NS
T_2 (30 min after premedication)	−0.276	NS	0.372	NS
T_5 (5 min after ERCP induction)	−0.758	$P = 0.0005$[a]	−0.675	$P = 0.001$[a]
T_7 (15 min after ERCP induction)	−0.718	$P = 00005$[a]	−0.847	$P = 0.0005$[a]
T_9 (entry to recovery unit after ERCP)	−0.585	$P = 0.007$[a]	−0.498	$P = 0.025$[a]
T_{10} (recovery unit 60 min post-ERCP)	0.076	NS	0.076	NS

[a]Significant negative correlation between sedation scales (mRSS and BIS) in group M and group T as determined by Spearman's correlation coefficient.

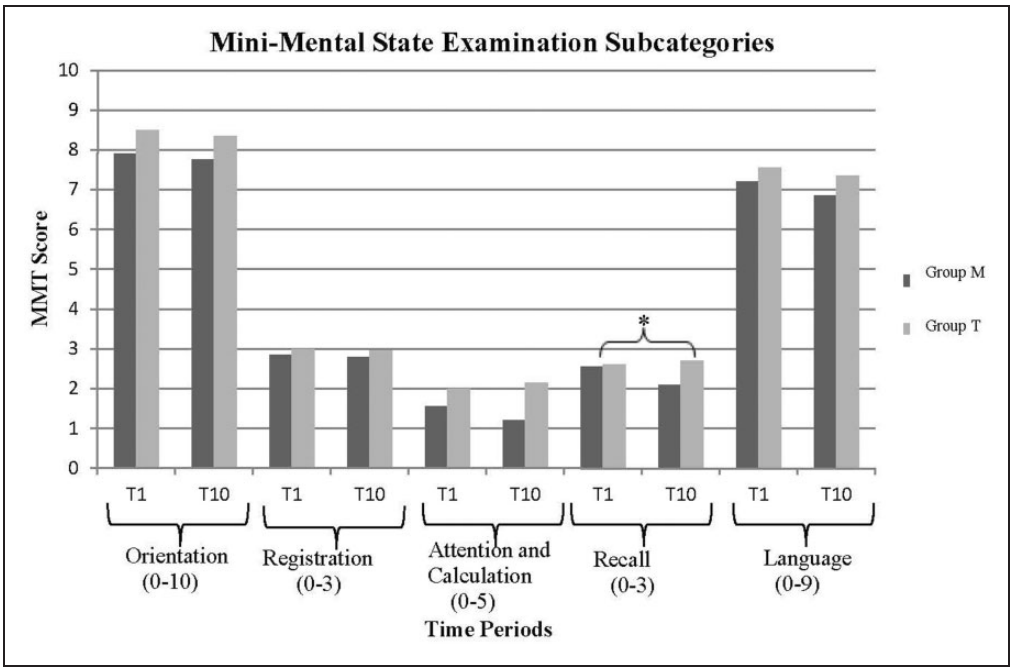

Figure 4. Mini Mental Test (MMT) subcategory scores in patients who received premedication with 0.15 mg/kg midazolam orally (group M, $n = 20$) or 1 mg/kg tramadol orally (group T, $n = 20$) prior to undergoing endoscopic retrograde cholangiopancreatography (ERCP). The MMT comprises five subtests: orientation (maximum 10 points), registration (three points), attention and calculation (five points), recall (three points) and language (nine points) for a total score evaluated out of 30. *$P = 0.024$ (χ^2-test).

Table 4. Recovery characteristics, patient and physician sedation satisfaction scores, and treatment side effects in patients who received premedication with midazolam (group M) or tramadol (group T) prior to undergoing endoscopic retrograde cholangiopancreatography (ERCP).

	Group M ($n = 20$)	Group T ($n = 20$)
Aldrete score (post-ERCP)	9.8 ± 0.2	9.9 ± 0.3
NRS Pain Score (post-ERCP)	3.1 ± 1.9	1.8 ± 0.2
Patient satisfaction score 3, excellent	18 (90)	15 (75)
Endoscopist satisfaction score 3, excellent	15 (75)	18 (90)
Patient's preference for premedication during next ERCP (yes/no)	19/1	18/2
Side effects		
Desaturation	5 (25)	2 (10)
Apnea	5 (25)	1 (5)
Hypertension	1 (5)	7 (35)
Hypotension	1 (5)	0
Tachycardia	17 (85)	17 (85)
Bradycardia	0	0
Inadequate sedation	6 (30)	9 (45)
Excess sedation	2 (10)	0
Agitation	1 (5)	4 (20)
Nausea/vomiting	4 (20)	4 (20)
Allergy/itching	0	0

Data are presented as mean ± SD or *n* (%) patients.
No statistically significant between-group differences; $P \geq 0.05$ (χ^2-test).
Patient and endoscopist sedation satisfaction scores evaluated as: 0 = bad, 1 = medium, 2 = good, and 3 = excellent.
NRS: numerical rating scale (pain).

infusion (0.1–0.15 μg/kg per min) in ERCP procedures.[10] Remifentanil was also used in the current study for analgesia and sedation although a dose of 0.20 μg/kg per min was employed.

In endoscopic procedures, premedication may have advantages such as reduction in drug demand for sedation, anxiolysis and induction and contribution to haemodynamic stability in conscious sedation procedures.[12] Outpatient procedures like ERCP, however, require that premedication drugs should be short acting, have sedative and analgesic contributions, not delay recovery and have minimal effect on cognitive function. As a consequence, benzodiazepines and analgesics are frequently used for this purpose.[13,14]

A limited number of studies have evaluated premedication in ERCP and differing conclusions have been drawn regarding the sedative contributions of benzodiazepines. In one study, 7.5 mg midazolam orally 30 min prior to ERCP conducted under propofol sedation was shown to be associated with a reduction in desaturation as a consequence of a decreased need for propofol; in addition, a positive synergistic effect of both drugs was noted with respect to anxiolysis.[13] Another study, however, demonstrated that premedication using 1 mg lorazepam orally in patients undergoing ERCP had no advantage in decreasing sedative needs and increasing haemodynamic stability.[14]

A previous randomized, double-blind, placebo-controlled trial compared the sedative effects of oral premedication with 7.5 mg midazolam with 150 μg clonidine administered 60–90 min prior to induction of

anaesthesia in healthy subjects undergoing elective surgery.[15] In this study, BIS values were significantly decreased in midazolam-treated subjects compared with placebo-treated subjects at 60–90 min after administration of premedication, upon entry to the post-anaesthesia care unit (PACU) and 60 min after entry to the recovery room. No significant change was, however, observed in sedation scores. Inconsistency may be detected between BIS and sedation scores but the reason for this is not clear.[15] In contrast, the present study demonstrated a correlation between BIS values and sedation scores. The current study used similar midazolam doses to those employed in the study by Paris et al.[15] but levels of sedation were lower. This may be due to residual benzodiazepine sedative effects. In the previous randomized study in which the average surgery time was more than 120 min, no residual sedative effect with respect to BIS values was observed after 120 min in the PACU in midazolam-treated subjects. No sedative effects were observed after 60 min in the PACU in both treatment groups in the current study.

Tramadol is also used as premedication for general anaesthesia and sedation although its use is not as widespread as midazolam.[16–18] Oral tramadol has been previously compared with midazolam as a paediatric premedication or in dental surgery.[18] Use of tramadol premedication in gastroenterological procedures has been investigated although no follow-up assessment of any sedation/analgesia scale was performed.[16] A previous placebo-controlled study demonstrated that tramadol premedication (100 mg orally) significantly decreased anxiety scores and analgesic need in patients undergoing surgical extraction of the mandibular third molar.[17]

Endoscopic retrograde cholangiopancreatography is generally planned as an ambulatory procedure. POCD is a relatively frequent occurrence that may negatively affect recovery and discharge after outpatient interventions. It can be defined as a 20% decrease in psychomotor test (e.g. Digit-Symbol-Substitution Test (DSST), Trieger Dot Test and MMT) scores from preoperative values.[19] Therefore, it is important to consider the effects of drugs used in anaesthesia and premedication on POCD. The incidence of POCD has been reported to range between 7% and 60% depending on the patient groups or procedure type investigated.[20] Studies have shown that cognitive function and psychomotor performance decreased significantly after monitored anaesthesia care and after general anaesthesia when sedative drugs and/or analgesics were used.[21] Patient discharge is usually planned within 2–3 h following interventional and endoscopic procedures but the effects of a medication on POCD plays an important role in determining when to discharge a patient, particularly after with ambulatory surgery with sedoanalgesia. Findings from the International Post-Operative Cognitive Dysfunction Study-1 demonstrated that rates of POCD were 25.8% in the first week following surgery and 9.9% in the third month.[5]

The effects of premedication on postoperative cognitive function are investigated when patients are fully conscious using neuropsychological tests performed both pre- and postprocedure.[7] The MMT is one of the most frequently used tests in the evaluation of early postoperative cognitive function or psychomotor recovery quality, with an MMT score of <25 regarded as indicating POCD at Day 1.[7,22] Subtests (e.g. tendency, registration memory, attention and calculation, recall and language) help to evaluate different cognitive functions; anaesthetic agents especially have a negative effect on memory. A study in elderly patients undergoing cataract surgery demonstrated that there was a correlation between deterioration in postoperative memory

performance in Luria tests and the first benzodiazepine dose.[23] In studies performed in healthy subjects, it was suggested that midazolam might be a key drug in the development of prolonged psychomotor and subjective impairment;[21,24] impairment in hand-eye coordination was found to continue even at 75 min after administration of midazolam.[21] Another study demonstrated that 5 mg diazepam administered intravenously before gastrointestinal endoscopy caused significant impairment in cognitive function compared with control patients in the early period (30 min), which was independent of blood drug level, patient age and plasma albumin levels.[25]

Preferred drugs for premedication prior to endoscopic procedures are those with short-term effectiveness that contribute to sedation and/or analgesia but that do not delay recovery. Some studies assert that discharge is not delayed with benzodiazepines in outpatient surgeries. In one evaluation in elderly patients who underwent cataract surgery under local anaesthesia, 0.049 mg/kg midazolam oral premedication provided adequate sedation and cognitive functions were protected compared with controls.[26] The authors of this study recommended midazolam premedication because no differences in numerical and verbal memory and concentration tests were observed during the early postoperative period (120 min) and it was well tolerated with respect to vital findings.[26] In another study, it was reported that the incidence of deep sedation and desaturation increased preoperatively following premedication with intravenous midazolam premedication in geriatric patients although mental and psychomotor recovery was not affected in the early postoperative period (60 min and 120 min).[27] Similarly, when intravenous midazolam (2 mg), fentanyl (50 μg) and/or propofol (35 mg) was administered to healthy subjects, no clinically significant psychomotor impairment was observed at 180 min and 240 min postinjection.[21] In a meta-analysis of premedication studies that involved use of benzodiazepines for prevention of presurgery anxiety, no delay in discharge time was observed; in some of the included studies it was reported that despite some minimal impairment in psychomotor function, this did not delay discharge.[28]

There are few data available regarding the postoperative cognitive effects of tramadol used as premedication. In the limited number of studies in the literature, cognitive function was investigated in patients who were received tramadol for postoperative analgesia. In one study, it was shown that postoperative tramadol was an important risk factor for POCD in patients aged >75 years who underwent major abdominal surgery.[29] Results from another study that evaluated the performance side-effect profile of high and low dose oral tramadol (200 mg or 50 mg four-times daily) in subjects being treated for opioid dependence, demonstrated that lower doses of tramadol were well tolerated in cognitive and psychomotor tests including DSST.[30]

In the present study, a decrease in total MMT score and all subcategories was determined in the midazolam group at 60 min post-ERCP with respect to baseline, but this did not reach statistical significance. Although there was a decrease in MMT total score in the tramadol group, no decrease was observed in 'memory' (recall) subcategory. A significant impairment was determined in the recall subcategory in patients who received tramadol as premedication compared with patients who received midazolam premedication.

In conclusion, premedication with midazolam in patients undergoing ERCP provides more effective sedation compared with tramadol premedication but is also associated with in memory. With respect to POCD, it was determined that cognitive function in the early postoperative period

was generally maintained and satisfying procedure comfort was provided with both drugs. While midazolam may be preferred for premedication for ERCP due to more effective sedation, clinicians should be prepared for dysfunction in the recall subcategory of the MMT in the post-procedure period.

Declaration of conflicting interests

The author(s) declare that there is no conflict of interest.

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