EVALUATION OF REMIFENTANIL IN ENDOSCOPIC RETROGRADE CHOLANGIO-PANCREATOGRAPHY

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Background and objective: Endoscopic retrogade cholangio-pancreatography (ERCP) is a painful procedure that requires transient analgesia and conscious sedation. Remifentanil an ultrashort, very potent narcotic, is eliminated by plasma esterases, and does not interfere with liver function. It does not accumulate and is free of residual depression.

Our aim is to find out if remifentanil can provide safe and effective sedation in ERCP, without undue technical difficulty secondary to sphincter spasm.

Patients and Methods: Thirty five patients, ASA I-II and III, scheduled to undergo elective ERCP were divided randomly in two groups: Midazolam-remifentanil group (group I), received remifentanil a loading dose of 0.2 μg/Kg/min over 5 minutes and a maintenance dose of 0.1-0.15 μg/Kg/min to achieve an adequate level of sedation and analgesia. Midazolam-fentanyl group (group II), received intermittent doses of midazolam and fentanyl guided by level of sedation. All patients were premedicated with midazolam 0.05 mg/kg IV, in divided doses as per patient tolerance, before starting the procedure. Sedation was assessed depending on Ramsey scale of sedation. SpO2, blood pressure, heart rate, respiratory rate, dosages of the medications, peroperative amnesia and operative time were recorded. Operator and patient satisfaction were rated on a scale of 1 to 4.

Results: There were statistically significant differences in the level of sedation ($p = 0.003$), patient satisfaction ($p = 0.01$) and the amount of

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midazolam used ($p < 0.01$) in favor of group I. Operator satisfaction was the same in the two groups. There was no statistically significant difference between the two groups regarding the peri-operative amnesia. The technical difficulty (catheterization of ampulla, duration of procedure, need of parasympatholytics…) was comparable in the two groups, as judged by the operator.

There was one case of mild desaturation in group I that responded to stimulation. No other respiratory or cardiovascular events were noted.

Conclusion: We recommend remifentanil in ERCP. Vigilance, however, must be exercised in titration and supervision of patients.

Keywords: Cholangio-pancreatography, Endoscopic Retrograde, remifentanil, conscious sedation.

Introduction

Endoscopic retrograde cholangio-pancreatography (ERCP) is a painful procedure that requires transient analgesia and sedation. Techniques used to achieve this goal implemented a variety of protocols including; among others', combinations of narcotics, benzodiazepines and propofol.

Remifentanil is an ultrashort acting, synthetic opioid. It has a methyl ester linkage and is metabolized by nonspecific blood and tissue esterases[1,2]. In adult patients, it has a rapid clearance (CL) and short terminal half-life ($T_{1/2}$), approximately 4 min that is independent of infusion duration[3] and of hepatic and renal function[4,7]. The resulting carboxylic acid metabolite, GR90291, has approximately 1/4, 600 the potency of remifentanil as a micro-opioid agonist in anesthetized dogs[8]. In humans, GR90291 is eliminated primarily via renal excretion with a terminal half-life of approximately 1.5-2 hours[2].

Low doses of remifentanil were used for conscious sedation, results in analgesia with negligible changes in neurocirculatory end-points[9], and should provide near ideal conditions for this procedure, provided sphincter spasm does not lead to detectable clinical difficulty. The narrow

margin of safety regarding depression of spontaneous respiration should be considered rigoursly.

Our aim is to find out if remifentanil can provide safe and effective sedation in ERCP.

Patients and Methods

After institutional ethics committee approval and, written informed consent, we studied 35 patients, (24 to 93 yrs, ASA physical status I-II and III) in a prospective, randomized manner. All patients underwent elective ERCP. Exclusion criteria included patients with allergies to the drugs being used, with increased intracranial pressure, who are heavier than 150% of their ideal body weight, with severe cardiovascular or respiratory diseases (ASA grade IV or higher), a history of drug abuse and long term use of benzodiazepines or tricyclic antidepressants.

All patients fasted for at least 6 hours before the procedure.

Each patient arrived to the endoscopy unit with an IV line. SpO2 sensor and blood pressure cuff were applied to the patient. Oxygen was administered by nasal cannula (3 l/min).

All patients were premedicated with midazolam intermittent up to 0.05 mg/kg IV before starting the procedure. Patients were randomly assigned to two groups:

Group I

Midazolam-remifentanil, 18 patients to receive remifentanil for maintenance had another IV gauge #22 cath installed for uninterrupted administration of remifentanil.

The latter was started at a loading dose of 0.2 μ/Kg/min over 5 minutes and maintenance of 0.1-0.15 μg/Kg/min in order to achieve an adequate level of sedation and analgesia.

Group II

Midazolam-fentanyl group, 17 patients received additional doses of

midazolam and intermittent fentanyl to achieve an adequate level of sedation.

Elderly patients received reduced doses (30-50% reduction).

Prior to endoscopic manipulation, every patient received topical anesthesia of the pharynx with lidocaine 2% spray. During the procedure SpO2, blood pressure, heart rate, respiration, dosages of medications and operative times were recorded.

Verbal contact with the patient was maintained to assess the degree of comfort and response to stimulation.

Sedation was assessed depending on Ramsay scale of sedation. Propofol 2 mg/kg/hr was added to this protocol in cases of inadequate sedation.

Agitation or other problems were noted.

At the end of the procedure the infusion of remifentanil was stopped.

Operator and patient satisfaction were rated on a scale of 1 to 4 (4 is the ideal and 1 is the worst). Recovery time was also monitored.

Patients were visited 4 hours later on the floor to assess their satisfaction, amnesia and the presence of side effects.

Statistics

Continuous parameters were tested with the *t*-test for independent samples and Fisher's exact test for categorical variables. Correlation was done using Pearson's test. All tests are two-tailed with a confidence level of 95% ($P < 0.05$). Consequently, significances of $P < 0.05$ reflect the probability of differences that can at best be used for generating hypotheses, but do not prove them.

Results

The two groups were comparable with the respect to demographic data: age, sex, and duration of the procedure (Table I).

Table I

Patient demographic data

Groups	Group I (n = 18 patients) [Remifentanil]	Group II (n = 17 patients) [fentanyl]
Age yr (mean ± SD)	61 ± 17	64 ± 18
Sex (% female)	78%	71%
Operative time (min) (mean ± SD)	64 ± 25	53 ± 23

Data are presented as mean ± SD.

There were statistically significant differences in the level of sedation (p = 0.003) and patient satisfaction (p = 0.01) in favor of group I. No correlation was found between age, sex and patient satisfaction or sedation level. Operators were satisfied equally regarding the two groups. The amount of midazolam used during the procedure was significantly lower in the remifentanil group (p < 0.01) (Table II), nonetheless this did not affect inadvertently the quality of amnesia. Three patients in the fentanyl/midazolam group did not support the procedure and propofol 2 mg/kg/hr was added to obtain an adequate level of sedation.

Table II

Statistical data

Groups	Group I [Remifentanil]	Group II [fentanyl]	p value
Patient sedation level	4.9 ± 0.9	3 ± 1.9	0.003
Patient satisfaction	3.8 ± 0.5	3 ± 1.1	0.01
Operator satisfaction	4	3.7 ± 0.47	
Peroperative amnesia	39.9%	47.1%	0.738
Midazolam dosage	1.8 ± 0.4	3.4 ± 1.4	< 0.01

Data are presented as mean ± SD.

Continuous parameters were tested with the *t*-test for independent samples and Fisher's exact test for categorical variables. Correlation was done using Pearson's test. All tests are two-tailed with a confidence level of 95% ($P < 0.05$).

There were statistically significant differences in the level of sedation measured depending on Ramsey sedation scale (p = 0.003) and patient satisfaction (p = 0.01).

Operator satisfaction was the same in the two groups.

There was no statistical significant difference between the two groups regarding the peri-operative amnesia.

There was significant difference in the amount of midazolam used during the procedure between the 2 groups (p < 0.01).

All patients in the remifentanil group had a recovery time less than 15 minutes while only 64.7% in the fentanyl group did (Table III).

Table III
Recovery time post Remifentanil and Fentanyl

	RECOVERY TIME < 15 min	RECOVERY TIME > 15 min
Group I REMIFENTANIL (N = 18)	18 (100%)	0
Group II FENTANYL (N = 17)	11 (64.7%)	6

The vital signs in the two groups (respiratory rate, pulse and blood pressure) were maintained, except for one case of mild oxygen desaturation 10% in remifentanil-midazolam group that corrected rapidly upon stimulation.

Discussion

Endoscopic retrograde cholangio-pancreatography (ERCP) is being used widely to diagnose and treat several biliary and pancreatic pathologies. Being less invasive than surgery, it has become the standard of care in a multitude of indications[10]. This procedure entails manipulation of the biliary tract in patients who already have hepato-biliary and pancreatic derangements. Besides the discomfort of the endoscope, pain due to interventions (ex: sphincterotomy, biliary dilatation) must be alleviated.

Several techniques have been implemented for the analgesia and sedation of such patients: narcotics for pain, hypnotics for patient comfort and benzodiazepines for amnesia. Remifentanil, an ultra-short opioid is herein evaluated.

Remifentanil, an ultra-short acting opioid, that does not depend on liver for metabolism, seems to be a good alternative, as it offers titrable analgesia without putting an extra burden on an already diseased liver. The hemodynamic stability that the drug incurs is an added benefit. In

addition, the expected fast recovery would be an advantage in terms of discharging the patient, especially in ambulatory cases. A couple of caveats need to be precoutioned.

The narrow margin of safety concerning depression of spontaneous respiration must be considered seriously.

Another disadvantage to consider would be the constrictive effects of morphine derivatives on the ampulla of Vater. However, if this does not surface as an added difficulty, then this possible drawback will not outweigh the advantages already mentioned.

This study showed statistically significant differences in terms of better sedation, better patient satisfaction and comparable amnesia at lower midazolam doses, in favour of remifentanil. The operators were satisfied with the adequate working conditions as concerns patients' sedation and cooperation provided in group I, however there was no statistical difference between the two groups (Table II).

All patients were fully awake and comfortable within 15 minutes after discontinuation of remifentanil vs. 64% in group II, which is an added benefit in terms of fastracking of patients. No patient in the remifentanil group needed additional intervention, whereas three patients in group II needed additional propofol in order to achieve adequate sedation.

The incident of mild desaturation, mentioned earlier, that occurred in one patient who received remifentanil emphasizes the need for extreme caution with the use of such a potent narcotic on patients breathing spontaneously.

No other untoward cardiovascular and respiratory events were noted in both groups.

Conclusion

Monitored anesthesia care for patients undergoing ERCP with continuous remifentanil after premedication with midazolam provides a pain free protocol with excellent patient sedation, satisfaction, amnesia,

operator satisfaction and very rapid return to consciousness, with no apparent increased technical difficulty secondary to sphincter spasm.

We recommend this technique, however vigilance must be exercised in titration and close supervision of patients.

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