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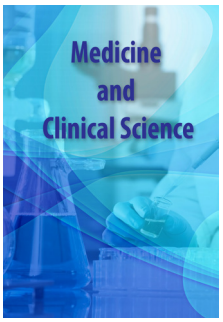
Original Article



Study of the respiratory depression during an analgosedation technique combining remifentanil and ketamine in TCI for oocyte retrieval

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Abstract

Introduction: Various methods of analgesia/anaesthesia have been validated for oocyte retrieval. In our institution, we administer remifentanil in target controlled infusion-mode (TCI), to maintain a score on the visual analogue scale (VAS) of less than 30mm. However, the incidence of respiratory depression is still significant. Our aim was to assess whether the addition of ketamine could reduce the number of respiratory events. Methods: In this prospective, non-randomized, uncontrolled study, 20 women were divided in two groups of ten: group 1 received ketamine at a target plasma concentration (Cp) of 150 ng/ml and group 2 of 200ng/ml. Our main outcome measure was the incidence of adverse respiratory events in relation to remifentanil and ketamine concentrations. Secondary outcome measures include sedation levels, dosage of ketamine-Cp, the accuracy of the Clements 250 pharmacokinetic model, post-operative side effects, intraoperative pain, the duration of the procedure, the outcome of the procedure and patient satisfaction. Results: In patients who experienced adverse respiratory events, both groups combined, remifentanil-consumption was higher (0.167 ± 0.055 mcg/kg/min versus 0.114 ± 0.059 mcg/kg/min, p-value 0,043) and measured ketamine was lower than the predicted Cp, although insignificant (0,020 ± 0.004 versus 0.024 ± 0.006, p-value 0,23). The difference in the incidence of adverse respiratory events in both groups was not significant (30% of bradypnea in both groups). The Clements 250 pharmacokinetic model predicted the ketamine-Cp accurately (bias of -7,25 and inaccuracy of 24,6). Post-operative side effects, patient satisfaction, the duration of the procedure and intra-operative pain levels were comparable in both groups. Conclusion: The association of subanaesthetic doses of ketamine with remifentanil for oocyte retrieval permitted a reduction of remifentanil consumption and adverse respiratory events, but no prevention. However, their incidence was higher when the predicted ketamine-Cp was not reached, and consequently more remifentanil was needed. Further studies at progressively higher target-Cp of ketamine in association with remifentanil should be conducted, under continuous anaesthetic surveillance.

Introduction

Along with the evolution of surgical techniques for assisted reproductive technologies, anaesthetic techniques have also advanced. Various methods of pain relief have been approved: general anaesthesia (GA), conscious sedation, neuraxial anaesthesia, paracervical block or different combinations of these [1]. Among these, conscious sedation is widely accepted. In the United States, it has been chosen for 95% of oocyte retrievals [2]. Another study reports high patient satisfaction and 86% of the women would opt for conscious sedation if a second procedure would be required [3]. Several concerns need to be taken into account when choosing the method of analgesia. First, the agent should be easy to administer and to monitor. Also, since the pain is rather intermittent than continuous, a short-acting substance is preferable [1]. It should also grant quick recovery, without severe post-operative side-effects, and provide adequate pain relief, without impairing normal breathing. Finally, it should have no detrimental effects on the outcome of the pregnancy [4]. Our protocol at the Erasme Hospital, Brussels, is based on conscious sedation, with low doses of alprazolam and midazolam, followed by a remifentanil-TCI [5]. By adjusting the effect-site target concentration (Ce) of remifentanil, we attempt to maintain a pain level on the VAS less than or equal to 30 mm throughout the procedure. Although this potent short-acting opioid agonist offers adequate analgosedation, episodes of bradypnea and desaturation still occur frequently.

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During a previous randomized, controlled study in our institution by Morue et al., an attempt has been made to reduce the incidence of respiratory depression by adding low-dose ketamine to the protocol in order to reduce the remifentanil-Ce (effect site concentration) (ketamine-group: target ketamine-Cp (plasma concentration) of 100 ng/ml associated with remifentanil, control group: remifentanil alone). However, the dose of ketamine proved insufficient to significantly lower remifentanil-consumption [5]. Our primary objective was to assess whether the addition of progressively higher pharmacokinetically predicted ketamine-Cp up to 200 ng/ml allows a notable reduction of the amount of remifentanil administered, to avoid respiratory events, while preventing excessive sedation levels. We equally evaluated patient satisfaction and the incidence of post-operative side-effects. Finally, by obtaining a ketamine-dosage in the patients' blood samples, we were able to assess the accuracy of the pharmacokinetic model used for our study (Clements 250) [6]..

Methods

This prospective, non-randomized, uncontrolled trial was conducted at Erasme, a tertiary care hospital in Brussels. After obtaining the Ethics Committee approval of the Erasme Hospital (number P2018/016) and ClinicalTrial.gov number NCT03458143, we started recruiting patients. Informed consent was obtained the morning of the procedure, before the patients took their premedication.

We included 20 women who underwent oocyte retrieval from the 13th of February until the 15th of March 2018. Exclusion criteria were a BMI over 30, and patients with endometriosis. Women with contraindications to ketamine (psychiatric disorder, coronary artery disease, glaucoma, increased intracranial pressure or thyrotoxicosis) were equally excluded.

Protocol failure was established as follows: excessive sedation due to adjunction of other drugs (e.g. propofol), necessity for ventilatory support (airway manipulation or facemask), and necessity to follow the standard protocol (i.e. remifentanil alone) due to technical difficulties (e.g. pump failure).

The patients were divided in two groups: the first 10 patients we recruited (Group 1) received ketamine at a target-Cp of 150 ng/ml in TCI mode, based on the Clements 250 pharmacokinetic model [6]. To the following 10 patients (Group 2), we administered ketamine at a Cp of 200 ng/ml. Before the procedure, a fasting period of 6 hours was required. At arrival in the operating room (OR), standard haemodynamic monitoring was connected to the patient (heart rate, non-invasive blood pressure (NIBP), pulse oximeter and a 3-lead ECG). An EEG bispectral index (BIS) was used to monitor the level of sedation. To follow the respiratory rate, patients received 2L/min of oxygen through a duct connected to capnography (Capnoline, Medtronic).

Prior to the procedure, the enrolled patients received 1 g of paracetamol (Prodafalgan®), 10 mg of butyl-hyoscine (Buscopan®) and, according to their needs, 0.5 mg of alprazolam (Xanax®). Once a peripheral venous line was in place, all patients received 2mg of midazolam IV.

The continuous ketamine-infusion was then started. The Cp for the first 10 patients was set at 150 ng/ml, using the Clements 250 model with the Toolbox software program [5]. For the following 10, the Cp was set at 200 ng/ml. After the desired Cp was reached, a continuous infusion of remifentanil-TCI was initiated, using the pharmacokinetic model of Minto. The Ce for remifentanil at the start of the procedure was set at 1 ng/ml. After 2 minutes, the gynaecologists started the procedure. The pain level was assessed shortly after a painful incident took place (ovarian puncture or manual pressure applied on the abdomen).

The patient was asked to grade her pain with the help of the VAS, which was described to her during the recruitment. The aim was to maintain a value less than or equal to 30 mm. If the level of pain was higher, the target remifentanil-Ce was gradually increased by 1 ng/ml. If it was less than 30 mm, the remifentanil-Ce was decreased by decrements of 1 ng/ml. The ketamine target-Cp was left unchanged. Both TCI were stopped when the gynaecologists notified that the procedure was finished.

Respiratory depression was defined as a breathing rate of less than 8/min, with or without moderate or severe desaturation (SpO2 between 90 – 94% and less than 90% respectively). This was treated with verbal stimulation ("take a deep breath, madam").

The sedation level was assessed with the help of the Observer's Assessment of Alertness/Sedation (OAAS) Scale and the Ramsay Sedation Scale every 2 minutes until the procedure was finished.

A venous blood sample was taken from each patient at the end of the procedure for ketamine dosage, in the arm contralateral to the infusion. The dosage was done at the laboratory of the University Hospital of Ghent, with the help of mass spectrometry (Q-exactive by Thermo Fisher®). After the procedure, the total amount of remifentanil and ketamine the patient received, were duly registered.

When the oocyte retrieval was completed, the patient was transferred to the Post-Anaesthesia Care Unit (PACU). The necessity for supplementary analgesic treatment, to maintain a VAS of less than 30 mm, was recorded. At the Erasme Hospital, this consists of IV piritramide (Dipidolor®) titration or 1g of Paracetamol (Dafalgan®). Adverse effects, such as pruritus, postoperative nausea and vomiting (PONV), visual symptoms or hallucinations were also noted.

When the patient was transferred to her room, satisfaction was assessed. The following scale was used: 3) very satisfied 2) moderately satisfied 1) unsatisfied. Finally, the incidence of possible side effects (i.e. PONV, visual symptoms or hallucinations), was documented.

Statistical Analysis

Binary variables (satisfaction, proportions of tachycardia, hypertension, respiratory depression, supplementary post-operative analgesia...) were analysed with the Chi-squared test, whereas continuous data was treated with the help of a Student's t-test. All values are expressed in mean ± standard deviation, and p-values of <0,05 were defined as statistically significant. The model predictability was assessed through the standard Varvel criteria, using the median percentage error (MdPE) and the median absolute percentage error (MdAPE) [7].

Results

Among the 42 eligible patients between the 13th of February 2018 and the 15th of March at the Erasmus hospital, we recruited 32. Ten patients were excluded for not meeting the inclusion criteria (BMI > 30 and/or endometriosis), six women refused to participate. No patients had contraindications to ketamine. 26 patients were included in the study. The first ten patients were allocated to Group 1 (ketamine at 150 ng/ml), the following ten to Group 2 (ketamine at 200 ng/ml). In Group 1, five patients were excluded. One, because the gynaecologists found no oocytes to be harvested, therefore no ovarian puncture took place. Three patients were excluded due to technical difficulties (e.g. pump failure), and for one patient the provided analgesia was insufficient and deeper sedation was required. In Group 2, one patient was excluded post-procedure due to inadequate intra-operative pain level assessment, owing to a distinctive psychological profile. In total, the data of 20 patients were analysed (Figure 1).

No difference was observed as to demographic data (age, BMI), ASA status and Apfel score.

The incidence of hypertension (NIBP > 160/110 mmHg) and tachycardia (HR > 100bpm) was similar in both groups (20% had hypertension in both groups, p=1, 30% presented tachycardia in group 1 and 20% in group 2, p=0,61) (Table 1).

There was an increase in respiratory events for patients who necessitated a higher dose of remifentanil, since their blood-levels of ketamine hadn't reached the predicted Cp. The lower the measured ketamine-Cp, the higher the amount of remifentanil required, and consequently, the higher the incidence of respiratory depression (Figure 2).

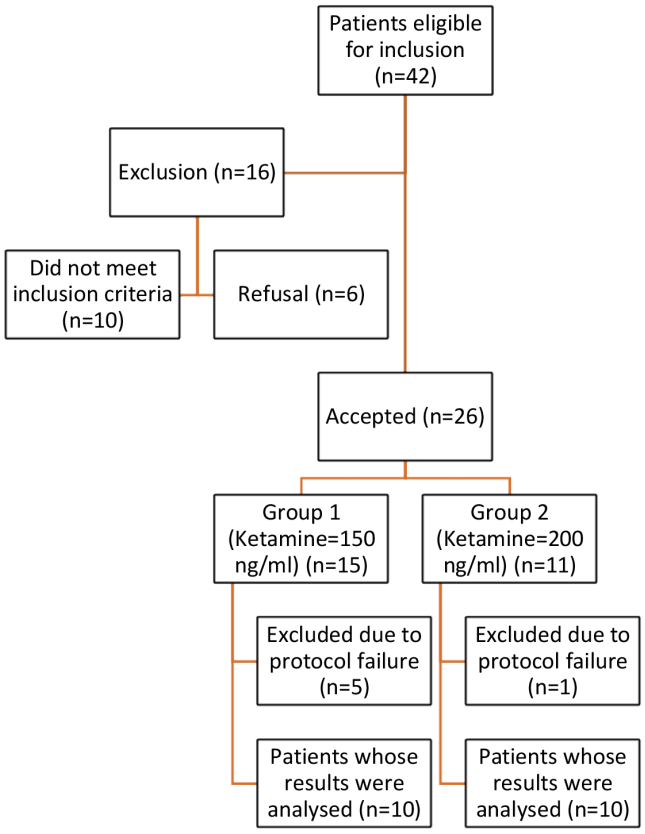

Figure 1. Flowchart

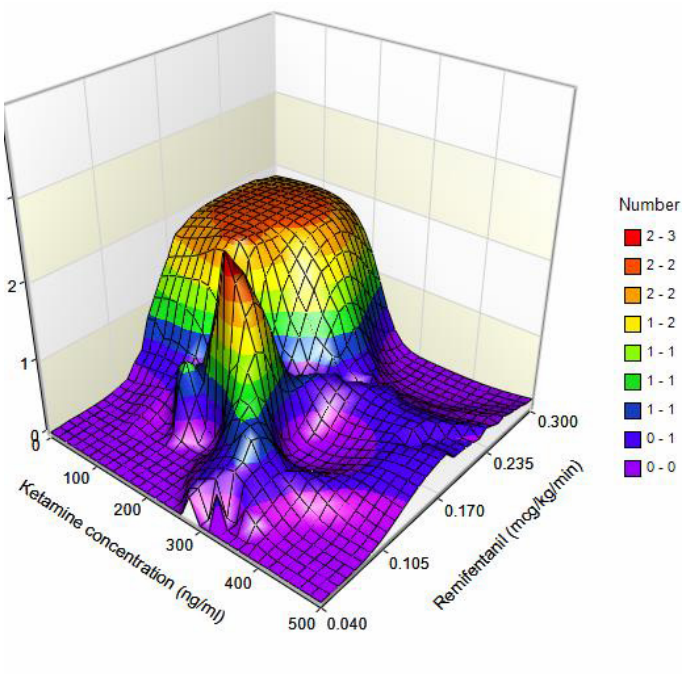

Figure 2. Surface plot of the number of respiratory events in relation to measured ketamine-Cp at the end of the procedure and total amount of remifentanil

	Group 1 (ketamine 150 ng/ml)	Group 2 (ketamine 200 ng/ml)	p-value
Age (years)	36,4 ± 1, 7	33,4 ± 3,9	0,19
BMI (kg/m^2)	23,9 ± 2,6	25, 6 ± 2	0, 33
% ASA 1	100%	90%	0,3
% ASA 2	0%	10%	0, 3
% ASA 3	0%	0%	1
Apfel score	2,2 ± 0,5	2,6 ± 0,4	0,25

Table1. Demographic data

	Patients with respiratory events	Patients without respiratory events	p-value
Ketamine infusion rate (mg/kg/min)	0.020 ± 0.004	0.024 ± 0.006	0,23
Remifentanil infusion rate (mg/kg/min)	0.167 ± 0.055	0.114 ± 0.059	0,043

Table 2. Consumption of remifentanil and ketamine in relation to the occurrence of respiratory

	Group 1	Group 2	p-value
Mean BIS	95,7 ± 1,05	93,9 ± 1,81	0,14
Minimal BIS	87,5 ± 3,64	84,1 ± 4,11	0,24
OAAS	4,22 ± 0,14	3,98 ± 0,23	0,09
Ramsay	2,72 ± 0,15	2,83 ± 0,21	0,41

Table 3. Sedation levels

Hypopnea occurred in six patients, among which four patients in both groups combined had lower measured blood levels of ketamine than predicted, and consequently necessitated more remifentanil (Ce > 2 ng/ml). When analysing the respiratory depression in both groups, in relation to the total consumption of remifentanil and ketamine, we notice that patients with respiratory events had a higher consumption of remifentanil than those without (Table 2).

Concerning respiratory events, there was no statistically significant difference between the two groups (30% in both groups, p=1). All patients responded to verbal stimulation following an episode of ventilatory impairment.

Low sedation levels were maintained throughout the procedure. (Table 3) All patients had an OAAS > 3 and a score on the Ramsay sedation scale fluctuating between 2 and 3. BIS values in both groups remained stable and did not show excessive sedation (< 80). When comparing sedation levels at the time the blood sample was drawn, to measured ketamine plasma concentrations, we observe that even when the predicted Cp was exceeded (>300 ng/ml), we always kept contact with the patient and there was no excessive sedation.

Regarding the Clements 250 model's predictability, the bias (MdPE) was -7,25 and the inaccuracy (MdAPE) valued 24,6. The mean measured concentrations are close to the predicted Cp for each group (164,49 ± 70,7 ng/ml in group 1, 208,47 ± 43,6 in Group 2).

Discrepancies were noted individually: two patients in Group 1 had higher ketamine concentrations in their blood (461,6 ng/ml and 204 ng/ml versus 150 ng/ml), and two patients did not receive the predicted Cp (35,7 ng/ml and 84,5 ng/ml versus 150 ng/ml). For two patients in Group 2, the measured ketamine-Cp was higher than predicted (341,9 ng/ml and 311,5 ng/ml versus 200 ng/ml) and one patient did not receive enough (123,5 ng/ml versus 200 ng/ml). The mean ketamine doses were 0,44 ± 0,03 mg/kg in group 1 and 0,6 ± 0,04 mg/kg in Group 2.

The incidence of post-operative adverse effects was low in both groups. The occupation time of the OR, the duration of the intervention (time from the first puncture until the gynaecologist notified the end of the procedure) and the duration of the ketamine-infusion were comparable in both groups.

The mean perioperative VAS was 2,8 in both groups. Postoperative analgesic use was low in both groups (1 patient in Group 1, none in Group 2). Postoperative antiemetics were consumed by 20% of the patients in group 1 and 50% in group 2. Patient satisfaction was high (90%) in both groups. Finally, the number of follicles punctured and harvested oocytes were also similar in both groups.

Discussion

Several studies have compared analgosedation techniques for oocyte retrieval, often yielding contradictory results. A Cochrane review by Kwan et al. showed that no method was superior to another. Conscious sedation however, was most favoured [1]. Several drugs have been used for this purpose, not without adverse respiratory events. The association of remifentanil and propofol for conscious sedation has proved to induce more severe respiratory depression, which needs correction by increased oxygen flow or manual respiratory assistance [8]. Various analgosedation techniques for oocyte retrieval use opioids. Wilhelm et al. studied the outcome of a remifentanil-infusion in a prospective study of 50 patients at a rate of 0,25 mcg/kg/min reaching average plasma-concentrations of 5-7 ng/ml in order to keep the women comfortable. This resulted in respiratory events in 10% of the patients [9]. A more recent study by Coskun et al. used a remifentanil-Ce of 1,5 ng/ml (Group 1), 2 ng/ml (Group 2) and 2,5 ng/ml (Group 3). However, because 26% of the patients didn't have adequate pain relief (VAS > 3) in Group 1, an increase of remifentanil was necessary. Moreover, in Groups 2 and 3, respiratory events were more frequent (9% for Group 2, 22 % for Group 3) [10]. In 2018, Morue et al. attempted to reduce respiratory depression due to remifentanil during oocyte retrieval by the addition of ketamine (Cp 100ng/ml, average dose of 0,24 mg/kg) [5].

The primary objective of this study was to analyse if by adding ketamine at higher doses would enable a reduction of remifentanil-Ce, thus decreasing perioperative episodes of respiratory depression, while maintaining a VAS < 30mm. Compared to Morue et al., where the occurrence of major respiratory events in the ketamine-group reached 60%, the incidence was lower in our study (30%).Moreover, because we measured the venous ketamine-Cp, we observed that ventilatory depression occurred in patients who did not reach the predicted Cp. This could explain the necessity for more remifentanil to keep the patient comfortable, causing more respiratory depression (Figure 2). Global remifentanil consumption in patients with or without respiratory events (0.167 ± 0.055 mcg/kg/min and 0,114 ± 0.059 respectively) was equally lower than Morue et al. (0,22 mcg/kg/min) (Table 2). The effects of the association of remifentanil and ketamine have previously been investigated. Fabbri et al. compared the administration of propofol-remifentanil (Group 1, n=162) versus propofol-remifentanil-ketamine (Group 2, n=160) for endoscopic retrograde cholangiopancreatography (ERCP), and found that with the addition of ketamine, the occurrence of respiratory depression was significantly lower (9 patients versus 25 patients in Group 1). Additionally, the ERCP had to be interrupted for 9 patients in Group 1, due to excessive sedation and needed manually assisted ventilation [11].

The use of ketamine in conscious sedation is justified for several reasons. First, it has been suggested that opioid-induced postoperative hyperalgesia might be influenced by N-Methyl-D-Aspartate (NMDA) receptors. Ketamine, an NMDA-antagonist, inhibits this pathway. It reduces hyperalgesia, and consequently, postoperative opioid consumption [12,13].

Second, low-dose ketamine may counteract the hypoventilation caused by opioids by increasing respiratory rate, in a concentration-dependent fashion. The mechanisms remain vague, but animal studies suggest the implication of NMDA-receptor in respiratory control [14]. The benefit of ketamine on ventilation has also been demonstrated in association with propofol, a strong respiratory depressant agent [15]. Finally, in view of opioid-sparing analgesia, particularly for tolerant patients and chronic opioid users, ketamine proves to be a good alternative [16]. In our study, compared to Morue et al., only 1 patient in Group 1 necessitated additional pain relief in the room and no patient in Group 2.

Regarding secondary effects of ketamine, none of our patients experienced hallucinations at doses of 0,44 ± 0,03 mg/kg in group 1 and 0,6 ± 0,04 mg/kg in Group 2 (infusion rates: Table 2), even when measured ketamine-Cp exceeded target-Cp set by the model. Three patients in Group 1 briefly had blurry vision before being transferred to the PACU. The linear dose-effect relationship between hallucinatory effects and steady-state plasma concentration (reaching 300 ng/l) was demonstrated in healthy volunteers [17,18]. However, more severe effects (anxiety, paranoia) seem to occur only at a Cp as high as 500 ng/ml [19]. Thus it is legitimate to consider increasing the ketamine-Cp in future studies at 250 - 300 ng/ml, to allow a low-dose opioid consumption, while remaining vigilant to the potential adverse effects. Nevertheless, the preoperative administration of a benzodiazepine is warranted, since it has shown a decrease in the incidence and gravity of unwanted postoperative events [20]. There is level 2 evidence that they can occur regardless of the rate, duration or dose of the ketamine-infusion [13].

Circeo et al. studied the level of sedation during oocyte retrieval associating fentanyl and propofol in a cohort of 50 women. Thirty-five patients needed ventilatory assistance (e.g. chin lift). The mean BIS-levels for these patients were at 66.52, whereas the group that had no respiratory aid, had a BIS-value of 56.38 [21]. With the association of remifentanil and ketamine, we did not reach levels of excessive sedation. We were able to maintain contact throughout the whole procedure, also when ketamine blood levels were higher than predicted by the model. Moreover, none of our patients needed manual ventilator assistance in case of respiratory depression. Verbal stimulation sufficed for each episode. Finally, in agreement with previous studies, patient satisfaction was high in our cohort [22].

Our study presented some limitations. The cohort consisted of only 20 patients, which doesn't represent the general population. A study on a larger group is needed to draw pertinent conclusions applicable in practice. Many patients were also influenced by a previous experience of anaesthesia, and expected to be completely unaware during the procedure. In future practice, it is highly recommended to explain the difference between conscious sedation and GA during the preoperative consultation, to avoid anxiety before the intervention and thus facilitate the task of the anaesthetist and the gynaecologist. We also did not randomize our patients and did not include a control group. However, we were able to compare our results to the study of Morue et al. in the same hospital [5]. The purpose of our study was first of all exploratory and pre-clinical, not comparative. We wanted to observe and describe the outcome of progressively increasing doses of ketamine to the current protocol, while remaining alert to potential side effects of ketamine. Since these did not occur significantly, we consider it reasonable to increase target ketamine-Cp incrementally in future studies (250 ng/ml, 300 ng/ml). The difference between the

2 groups in terms of target ketamine-Cp is too little to draw pertinent conclusions (150 ng/ml versus 200 ng/ml). Nonetheless, raising ketamine directly at a higher target-Cp (>300 ng/ml) implies the possibility of loss of patient contact due to excessive sedation. Since the risk of respiratory events under remifentanil is significant, losing patient contact would deem life-threatening for the patient.

The administration of midazolam might mask potential perioperative side effects due to ketamine. The depth of anaesthesia should be adapted according to patient anxiety and the skills of the operator. GA certainly allows the gynaecologist to harvest oocytes easier, but it is associated with prolonged occupation of the OR, longer recovery time, higher incidence of PONV and need for specialized equipment and trained staff [22].

Conclusion

In conclusion, the association of ketamine (0,44 mg/kg and 0,6 mg/kg) with remifentanil allowed a reduction of adverse respiratory events compared to Morue et al. Yet we were not able to entirely avoid them. Remifentanil-consumption was also lower. Both groups combined, the incidence of hypopnea was higher when the requested ketamine-Cp was not reached, and consequently a higher remifentanil-dose was necessary. In future practice, it is reasonable to incrementally raise the target ketamine-Cp (250 ng/ml, 300ng/ml) in order to reduce remifentanil-consumption, since its benefits largely outweigh the risks at subanaesthetic doses. Patient contact is kept at measured ketamine-Cp exceeding 200 ng/ml. Larger studies should be conducted in order to draw clinically significant conclusions regarding this protocol.

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