Comparison between local anaesthesia with remifentanil and total intravenous anaesthesia for operative hysteroscopic procedures in day surgery†

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Background. This study aimed at comparing total i.v. anaesthesia (TIVA) with monitored anaesthesia care (MAC) during day-surgery operative hysteroscopy regarding: operation time, time to mobilization and discharge, and patient satisfaction.

Methods. Ninety-one healthy women were randomized to MAC with paracervical local anaesthesia and remifentanil or to TIVA with propofol and remifentanil. Time from arrival to leaving the operating theatre, time from arrival in the recovery room to mobilization and discharge readiness, and patient satisfaction with MAC and TIVA were observed.

Results. Time from arrival to leaving the operating theatre showed no significant difference between groups (P = 0.6). The time to mobilization (MAC: 53 min [inter-quartile range (IQR) 40–83], TIVA: 69 min (IQR 52–96) (P = 0.017)) and the total time from arrival to discharge readiness (MAC: 118 min (IQR 95–139), TIVA: 138 (IQR 120–158) (P = 0.0009)) were significantly reduced for patients in the MAC group. More patients in the MAC group 45 (91.8%) than in the TIVA group 24 (64.9%) responded positively to the question: would you like to receive the same kind of anaesthesia for a similar procedure in the future? (P = 0.003).

Conclusions. Paracervical local anaesthesia combined with remifentanil is suitable for operative hysteroscopy in day surgery.

Keywords: ambulatory surgery; anaesthesia recovery period, hypnotics and sedatives; analgesics, opioid; conscious sedation; hysteroscopy; piperidines

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Operative hysteroscopic procedures such as polypectomy, endometrial ablation, and myomectomy are often performed in the day-surgery setting under general anaesthesia with propofol and remifentanil.1 The use of stand-alone local anaesthesia for these procedures has been shown to be inadequate, often leading to conversion into general anaesthesia or additional i.v. sedation,2 which suggests the routine use of i.v. sedation analgesia as a supplement to local anaesthesia.3 4

Remifentanil, a potent short-acting opioid, provides both analgesia and sedation and is easily adjustable and short lasting regardless of infusion time.5–7 Paracervical local anaesthesia has recently been documented to be a suitable method of pain control in women undergoing diagnostic hysteroscopy as outpatients.8 Sedation analgesia with remifentanil in combination with paracervical local anaesthesia for hysteroscopic operative procedures may reduce turnover time in the operating theatre, and enabling early discharge, while safety and patient satisfaction are maintained.

The aim of the study was to compare total i.v. anaesthesia (TIVA) with a combination of paracervical local anaesthesia and remifentanil sedation analgesia [monitored anaesthesia care (MAC)] during operative hysteroscopy in a day-surgical setting. Outcome measures were time in the operating theatre, recovery time and quality, time to mobilization and discharge, patient satisfaction, adverse events, and time to resume activities of daily living.

Methods

We included 91 women undergoing an operative hysteroscopic procedure (endometrial polyp, uterine fibroids, or endometrial ablation) at the Day Surgery Units of the Copenhagen
University Hospitals in Herlev and Hillerød, Denmark, from August 2008 through July 2010. The study was approved by the local Ethics Committee (jr. no. H-D-2008-031) and registered at Clinicaltrials.gov (Id. NCT00763789). All participants gave oral and written informed consent. We included healthy women [ASA physical status (PS) I or II] aged 18 yr or older speaking and reading the Danish language. Exclusion criteria were ASA-PS class ≥III, BMI ≥35, psychiatric illness with chronic medical treatment, non-cooperative patients, and patients taking sedatives and analgesics [except paracetamol or non-steroid anti-inflammatory drugs (NSAIDs)] within the last week before surgery. Patients with known allergy to NSAIDs, paracetamol, opioids, or amide local analgesics were excluded, as were patients undergoing otracheal intubation after preoperative assessment by the anaesthetist.

The study was designed a randomized clinical trial with parallel groups and no blinding of patients or of outcome assessors. Patients were randomized either to the monitored anaesthesia care (MAC) group: remifentanil sedation analgesia combined with paracervical local anaesthesia or to the TIVA group: total i.v. anaesthesia with propofol and remifentanil. The random allocation sequence was generated by shuffling opaque, sealed envelopes. We stratified patients to either polypectomy or endometrial ablation/myomectomy, since the duration of these surgical procedures might differ. Randomization and patient inclusion took place on the day of surgery immediately after arrival at the Unit. In order to secure allocation concealment, more sealed envelopes that were needed according to the sample size calculation were available.

**Anaesthesia**

All patients received oral premedication with lornoxicam (an NSAID) 8 mg and paracetamol 1 g. Dexamethasone 4 mg and ondansetron 4 mg i.v. were used for prophylaxis against nausea and vomiting depending on the presence of postoperative nausea and vomiting (PONV) risk factors identified by the same four senior anaesthetists at the preanaesthesia assessment before study inclusion. Anaesthesia was standardized in both groups. In the MAC group, the remifentanil infusion was initiated at 0.166 μg kg⁻¹ min⁻¹. When the patient was able to sense the effect of remifentanil (burning cheeks, dizziness, feeling surreal), the gynaecologist informed the patient was able to sense the effect of remifentanil injection starting at 0.5 μg kg⁻¹ min⁻¹ and a bolus of propofol 2–2.5 mg kg⁻¹ followed by propofol infusion at 5 mg kg⁻¹ h⁻¹. From this point, individual adjustments were allowed according to the study protocol. If permissible, the rate of the remifentanil infusion should be halved after 10 min and the propofol infusion rate reduced by a third after 15–20 min infusion time. Both remifentanil and propofol infusions were discontinued 4–5 min before the end of surgery.

The airway was managed with a laryngeal mask and volume controlled ventilation, FIO₂ ≥40%, in a circle system. Patients’ vital signs were continuously monitored with NIAP, pulse oximetry (PSO₂), HR, RR, and three-lead electrocardiography. Airway pressure, oxygen fractions, and inspiratory and end-tidal CO₂ fractions keeping the end-tidal CO₂ between 4 and 4.5 kPa were monitored in the TIVA group. The lowest systolic arterial pressure, PSO₂, HR, and RR during the procedures were recorded.

In both groups, surgery was performed by experienced gynaecologists specialized in hysteroscopic procedures and familiar with paracervical local anaesthesia.

Patients were monitored after operation in the recovery room using NIAP, PSO₂, and HR until they fulfilled the standard criteria for discontinuation of monitoring. The time to mobilization and the time to discharge were recorded, as were spontaneous reports of side-effects such as nausea or itching (yes/no). The time to mobilization was defined in the study protocol as ‘being able to get dressed and to be up and about’, discharge readiness was measured according to fulfilment of the standard criteria in the post-discharge scoring system (vital signs, activity level, nausea and vomiting, pain, and surgical bleeding). A case report form followed the patients and was continuously filled in during their stay at the Unit. Besides primary and secondary outcomes, patient characteristics, baseline data, and data recorded to ensure patient safety were also recorded in the case report form. The nurses at the day-surgery units assessed these outcome variables at arrival, every 15 min, at discontinuation of monitoring, and if any changes in the monitored variables occurred. The nurses were instructed to have extra focus on the patients participating in the trial in order to secure the correct measurement of the time-dependent outcomes.

The primary outcome was the time from arrival to leaving the operating theatre. Secondary outcomes were the time from entering the recovery room to mobilization and to discharge readiness.

At discharge, all patients were supplied with a questionnaire to be filled in at home. Questions addressed the patient’s satisfaction, whether they would like to receive the same kind of anaesthesia again, the time spans until...
the patient felt able to think clearly, to walk around normally, and to resume activities of normal daily living. Side-effects from anaesthesia (nausea and itching) occurring after discharge were recorded using a four-point scale (none/mild/moderate/severe); vomiting was recorded as yes/no. Surgical outcome was estimated graduating the vaginal bleeding 5–7 days after operation in relation to regular menstrual bleeding (more/less). In addition, we asked for consumption of pain medication due to pelvic pain or tightness. To ensure a high response rate to the questionnaire, all the patients were contacted by phone to obtain their answers. The questionnaire was developed and validated to ensure content validity and face validity.12–14

In a pilot-structured interview test, with seven respondents, carried out at the start of the study, we refined the questionnaire and clarified problems with wording and questions.

Statistics
Based on retrospective data of patients undergoing an operative hysteroscopy under general anaesthesia in the Day Surgery Unit, Herlev Hospital, we estimated the average time in the operating theatre to be 53 (16) min. The sample size was calculated as a 10 min reduction in time spent in the operating theatre was considered clinically relevant.

With a power of 80% and a 5% two-sided significance level, a sample of 40 patients in each group was needed. We increased the sample size by 20%, taking into account eventual drop-outs, ending up with 96 needed for the assessment.

All calculations were made using IBM SPSS Statistics, Release 19.0.0 (2010, IBM Corporation, Somers, NY, USA) or R statistical software, version 2.12.1 (2010, R foundation for Statistical Computing, Vienna, Austria).

Testing for normality of data was performed without pointing towards normal distribution. Therefore, non-parametric testing was performed. A χ² test was used for dichotomous covariates and the Mann–Whitney test for continuous covariates. Calculating significance for time intervals, we performed a correction for multiple testing by the Bonferroni–Holm method. All P-values are two-sided and those below 0.05 were considered significant. Intention-to-treat analysis was performed.

Results
We screened 310 women undergoing operative hysteroscopic procedures. Of these, 219 did not meet the participation requirements (reasons given in Fig. 1); 91 were included in the study.

Forty-nine patients were randomized to the MAC group and 42 to the TIVA group. The groups were comparable regarding age, BMI, smoking status, ASA class, type of hysteroscopy performed, and premedications (Table 1). Patients at the two Units did not differ in their baseline characteristics (data not shown). One patient in the MAC group was converted to general anaesthesia due to surgical difficulties and pain. However, she was still analysed according to her randomization group (intention-to-treat analysis). All patients were followed up regarding the primary outcome and only one did not receive the questionnaire to be filled in at home. The response rate to the questionnaire was 100%. During the study, no included patients dropped out. The results of the time intervals are shown in Table 2 and Figure 2. We found no significant difference between groups for the time from arrival to departure from the operating theatre (P=0.6). However, we found that both the median time to mobilization after entering the recovery room and the total median time from arrival at the operating theatre to discharge readiness were significantly shorter in the MAC group. Waiting time between being ready for discharge and leaving the Unit did not differ between the groups (Table 2). The actual operation time did not differ between groups, median values: MAC 15.0 min, TIVA 15.5 min (P=0.88). In the operating theatre, six (12.3%) of the 49 patients having MAC suffered from nausea; three of these patients vomited. In the recovery room, more patients in the MAC group suffered from nausea (11 (22.4%) (n=49) vs 2 (4.8%) (n=42) (P=0.016)) (Table 3). After discharge, nine patients in each group suffered from mild nausea, and two patients, both belonging to the TIVA group, reported severe nausea after discharge.

In the MAC group, 45 (91.8%) (n=49) vs 24 (64.9%) (n=37) in the TIVA group affirmed the question: ‘Would you like to receive the same anaesthesia technique for a similar operative procedure in the future?’ (P=0.003). The patients in the MAC group regained the ability to think clearly and to walk around normally faster than did patients in the TIVA group (Fig. 3). Results also showed a difference, though not a significant one, in favour of the MAC group in the time to resume activities of daily living. The extent of vaginal bleeding and consumption of pain medication during the first 5–7 postoperative days did not differ between groups (data not shown).

Data recorded to ensure patient safety (PsO₂, HR, NIAP, and RR) did not result in discontinuation of interventions (Table 3). None of the patients was sedated to a degree where they were not responding to verbal requests or became cyanotic, and at the present infusion rates, data recorded to ensure patient safety (PsO₂, HR, NIAP, and RR) did not result in discontinuation of interventions (Table 3).

Discussion
The most important finding of this study is that the time-saving potential of MAC is realized not in the operating theatre but rather in the recovery room. More patients in the MAC group were willing to receive the same anaesthesia technique in the future, despite suffering significantly more from nausea in the immediate postoperative period. This acceptability is crucial for the implementation of the technique.
Our finding that the time each patient spent in the operating theatre was similar in the MAC and TIV A groups did not support our initial hypothesis. We stipulated that saving 10 min in the operating theatre for every patient would make room for an additional hysteroscopic procedure per day. However, the results indicate that if any time was saved in the MAC group through avoiding recovery from anaesthesia, it was lost due to the initial procedure of sedation, administration of local anaesthesia, and other minor procedures, the actual operative time being the same. Furthermore, an experienced anaesthetist aligns the waking of each patient to the ending of the hysteroscopy and the preparation for their transfer to the recovery room.

Only one patient in our study found hysteroscopy under MAC to be totally unacceptable, necessitating conversion from MAC to TIV A. The reason was severe pain during the Hegar dilation of the cervical canal, indicating non-functioning paracervical blockade. Remifentanil sedation as part of an MAC regimen and an adjunct to regional anaesthesia has previously been shown to provide effective analgesia in a day-surgery setting during miscellaneous procedures.15–21 In a similar study comparing local and general anaesthesia for endometrial microwave ablation, 13% of the patients randomized to local anaesthesia converted to general anaesthesia and with 55% needing additional midazolam sedation.2 Our study demonstrates that for operative hysteroscopic procedures, a combination of remifentanil sedation with local anaesthesia provides effective analgesia.

The average time saved per patient through reducing the time to mobilization and discharge readiness for the MAC group in the Unit was estimated as 23 min. This was also the case in a study for colonoscopies comparing sedation analgesia with remifentanil/propofol to TIV A.22 Sedation caused much faster recovery and discharge readiness than TIV A. The faster recovery is thought to be a consequence of the pharmacokinetic properties of remifentanil.6,7

As in normal procedures, all the patients returned to the recovery room. However, several patients belonging to the MAC group very quickly felt clear headed and were able to walk around normally. The potential for bypassing the recovery room, thereby saving resources, is obvious but beyond the scope of this study.

Like other opioids, remifentanil has adverse effects including nausea, vomiting, itching, respiratory depression, chest
wall rigidity, bradycardia, and hypotension. Nausea was prominent in this study. Twelve percent of the patients in the MAC group had nausea in the operating theatre, and it remained a problem in the recovery room. Nausea during remifentanil sedation has been observed in studies with remifentanil as an adjunct to regional anaesthesia. This is a potential drawback for the remifentanil sedation regime. However, our finding of a lower incidence of nausea during remifentanil sedation suggests that the use of standard PONV prophylaxis may be beneficial. It is well known that nausea and vomiting extends the time until patients are ready for mobilization and discharge. In our study, patients without nausea were mobilized about 20 min earlier than those with it, although this finding was insignificant. In all cases, the nausea and vomiting caused by remifentanil was short lasting and in most cases disappeared during the stay in the recovery room. Nausea did not cause trouble to patients after they had been discharged and, despite PONV, more patients in the MAC group were in favour of this technique when asked about preferences. This is in accordance with previous observation of remifentanil used for sedation analgesia during colonoscopies. Willingness to receive the same technique in the future was also high, >90% in a study comparing propofol and remifentanil for MAC. The fact that patients in the MAC group were able to walk around and able to think clearly earlier may have contributed to the positive attitude towards the remifentanil sedation regime.

Limitations and strengths

The population in the present study was a selected one. Out of 310 patients screened for eligibility, 114 eligible patients refused to participate. The main reason for this was the preferences for a certain anaesthesia technique which can affect extern validity negatively. The women who were willing to go forward into randomization were highly motivated for participation in the study; this might have affected in a positive way the patients' tolerance for the monitored anaesthesia care method.

The exact number of PONV risk factors was not recorded. Also, the randomization should balance the unknown prognostic factors at baseline. However, all patients were scored for their risk of developing PONV as a part of daily routine by the same four senior anaesthetists at the preanaesthesia assessment and prophylactic antiemetics were prescribed according to PONV instructions. Prophylactic antiemetics were defined as a baseline value as were smoking status. None of these did differ between groups. We assume that no group had been more prone to PONV than the other, in accordance with the assumptions for randomization.

The original sample size calculation estimated that 80 patients were needed for the assessment of the primary outcome. During the study, no included patients dropped out and we therefore ended the inclusion after 91 patients.

### Table 1: Patient characteristics. *Numbers and proportions (%). §Median (IQR) [range]

<table>
<thead>
<tr>
<th></th>
<th>MAC group (n=49)</th>
<th>TIVA group (n=42)</th>
</tr>
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<tbody>
<tr>
<td>Stratification*</td>
<td></td>
<td></td>
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<tr>
<td>Endometrial ablation/myomectomy</td>
<td>17 (34.7)</td>
<td>16 (38.1)</td>
</tr>
<tr>
<td>Polyectomy</td>
<td>32 (65.3)</td>
<td>26 (61.9)</td>
</tr>
<tr>
<td>Hospital*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herlev</td>
<td>32 (65.3)</td>
<td>30 (71.4)</td>
</tr>
<tr>
<td>Hillerød</td>
<td>17 (34.7)</td>
<td>12 (28.5)</td>
</tr>
<tr>
<td>Age (yr)§</td>
<td>47 (44–52)</td>
<td>44.5 (40–56)</td>
</tr>
<tr>
<td>Body mass index§</td>
<td>24.8 (22.7–27.2)</td>
<td>25.5 (23.3–29.0)</td>
</tr>
<tr>
<td>Smoking status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>35 (71.4)</td>
<td>30 (71.4)</td>
</tr>
<tr>
<td>Smoker</td>
<td>14 (28.5)</td>
<td>12 (28.5)</td>
</tr>
<tr>
<td>ASA physical status*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA physical status class I</td>
<td>34 (69.4)</td>
<td>32 (76.2)</td>
</tr>
<tr>
<td>ASA physical status class II</td>
<td>15 (30.6)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>Operation*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial ablation/myomectomy</td>
<td>24 (49.0)</td>
<td>21 (50.0)</td>
</tr>
<tr>
<td>Polyectomy</td>
<td>25 (51.0)</td>
<td>21 (50.0)</td>
</tr>
<tr>
<td>Premedication* (yes/no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lornoxicam</td>
<td>(46/1) 48 (98.0)</td>
<td>(41/1) 41 (97.6)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>(46/3) 46 (93.9)</td>
<td>(38/3) 38 (92.9)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>(35/14) 35 (71.4)</td>
<td>(30/12) 30 (71.4)</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>(4/39) 4 (9.1)</td>
<td>(5/35) 5 (12.5)</td>
</tr>
</tbody>
</table>

### Table 2: Results. Time intervals related to patient flow for the MAC and TIVA groups, respectively. DSU, day-surgery unit. *Median and (IQR) [range]. All in minutes

<table>
<thead>
<tr>
<th></th>
<th>MAC</th>
<th>TIVA</th>
<th>P-value</th>
<th>P-value, corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in the operating theatre</td>
<td>43 (36–53) [22–92]*</td>
<td>41 (35–52) [25–75]*</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Recovery room—time to mobilization</td>
<td>53 (40–83) [18–192]*</td>
<td>69 (52–96) [24–215]*</td>
<td>0.017</td>
<td>0.034</td>
</tr>
<tr>
<td>Time from arrival in the operating theatre to discharge readiness</td>
<td>118 (95–139) [68–241]*</td>
<td>138 (120–158) [91–301]*</td>
<td>0.0009</td>
<td>0.0027</td>
</tr>
<tr>
<td>Time from discharge readiness to departure from DSU</td>
<td>21 (10–35) [0–165]*</td>
<td>25 (10–40) [0–128]*</td>
<td>0.8</td>
<td>—</td>
</tr>
</tbody>
</table>
A weakness of the study is the lack of blinding. However, attempts to blind it would have failed for several reasons. In the operating theatre, blinding was obviously not an option, and after operation, the organization of the Unit, with the nursing staff having very flexible workspaces, did not allow it. In addition, almost every patient could be judged as having

Fig 2 Time intervals related to the patient flow in the day-surgery unit, MAC and TIVA groups, respectively. *Total stay at the DSU (day-surgery unit): time from arrival in the operating theatre to discharge readiness. **Operating theatre: time from arrival to leaving the operating theatre. ***Recovery room: time from entering the recovery room to mobilization. MAC, monitored anaesthesia care; TIVA, total i.v. anaesthesia.
had MAC or TIVA just by looking at them on arrival in the recovery room.

Subjective outcome measures are more prone to be influenced by lack of blinding. The secondary outcomes, time to mobilization and discharge readiness, were assessed by the staff in the units. To reduce performance blinding, the term ‘being mobilised’ was strictly defined in the study protocol (‘being able to get dressed and to be up and about’). It

<table>
<thead>
<tr>
<th>Table 3 Nausea during and after operation and vital signs. Proportions and numbers (yes/no). P-value by two-sided $\chi^2$. *Median (range)</th>
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<tbody>
<tr>
<td>Nausea during operation*</td>
</tr>
<tr>
<td>Nausea in the recovery room*</td>
</tr>
<tr>
<td>Percentage reduction in systolic BP*</td>
</tr>
<tr>
<td>Lowest $P_{S02}$ *</td>
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<tr>
<td>Lowest HR*</td>
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<tr>
<td>Lowest RR*</td>
</tr>
<tr>
<td>Nausea during operation§</td>
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<tr>
<td>Nausea in the recovery section</td>
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</table>

Fig 3 Cumulative answers to the questions ‘When were you first able to walk around like you normally do?’ (a) and ‘When did you first feel able to think clearly?’ (b). MAC, monitored anaesthesia care; TIVA, total i.v. anaesthesia.

had MAC or TIVA just by looking at them on arrival in the recovery room.

Subjective outcome measures are more prone to be influenced by lack of blinding. The secondary outcomes, time to
was stressed to the outcome assessing nurses that the patients must be mobilized as soon as the requirement was fulfilled and it was the impression that the prescription was understood and followed. Discharge criteria followed the normal scoring system,\textsuperscript{11} the scoring performed at least every 15 min. The staff who cared for these patients in general showed them extra attention in order not to induce bias into the time measures. Nonetheless, performance bias could have led to both an under- or an overestimation of the time-saving effect of MAC.

We find external validity to be strengthened by the fact that the outcome assessing nurses only used the tools they normally use for assessing whether the patients were ready for mobilization or discharge.\textsuperscript{25} Conduction of the study took place in a daily clinical setting, the anaesthesia protocols reflecting daily practice. Overall, the findings of the study can be generalized to women having similar procedures as operative hysteroscopy in a day-surgery setting.

In summary, the main finding of the present study is that despite more nausea in the MAC group, patients show more willingness to have the same anaesthesia technique in the future. The total time spent in the Unit was 23 min less using MAC due to faster mobilization and discharge readiness. As such, MAC with remifentanil as a supplement to paracervical local anaesthesia provided effective sedation and analgesia without serious adverse events in healthy women undergoing operative hysteroscopic procedures in a day-surgery setting.

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Declaration of interest
None declared.

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Appendix
The remifentanil infusion rate is gradually reduced by 100 µg h\textsuperscript{−1} 10 kg\textsuperscript{−1} if one of the following safety parameters is satisfied:

- RR ≤ 8 for more than 2 min, provided that the patient does not obey appeals to breathe.
- SAT ≤ 95%, provided that the patient does not obey appeals to breathe.

Two minutes after a reduction in the infusion rate, a new evaluation of RR, SAT, and sedation score must be performed in order to assess the need for further reduction in remifentanil infusion rate.

The remifentanil infusion rate is gradually increased by 100 µg h\textsuperscript{−1} 10 kg\textsuperscript{−1} every second minute if the patient expresses pain (VAS score ≥ 30 mm) until the VAS score is ≤ 30 mm.

Only patients expressing pain either orally or by making grimaces or withdrawals to painful stimuli were asked to graduate their pain on a 100 mm VAS scale.

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