

Randomized double-blind comparison of remifentanil and alfentanil in patients undergoing laparoscopic cholecystectomy using total intravenous anesthesia

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Abstract

Background and Aims: To compare the use of remifentanil and alfentanil to suppress intraoperative adrenergic response of pain and the influence of these drugs on the recovery profile in patients undergoing laparoscopic cholecystectomy using a total intravenous anesthesia (TIVA) technique.

Material and Methods: One hundred patients undergoing elective laparoscopic cholecystectomy were randomized to be managed with either remifentanil (group R) or alfentanil (group A). During general anesthesia, we evaluated adrenergic responses to intubation to first surgical incision and over the surgical procedure. We also recorded time to first spontaneous breathing, time to successful ventilation, time to respond to verbal orders, and time to extubation.

Results: The R group reported a significantly lower number of responses to intubation and responses to first surgical incision (14% vs. 30%; $P = 0.013$ and 8% vs. 18%; $P = 0.037$, respectively). The event of one or more responses during the surgical procedure was also lower in the R group (56% vs. 70%; $P = 0.017$). Hypertensive response to surgical stimuli during the procedure was lower in the R group as well as a lower frequency of tachycardia episodes in this group (34% vs. 56%; $P = 0.033$ and 28% vs. 44%; $P = 0.041$, respectively). No differences were found between groups relating to the percentage of hypotensive episodes and no episodes of bradycardia were appreciated. Both groups were similar relating to recovery times: time to the first spontaneous breathing, time to successful ventilation, time to respond to verbal orders, and time to extubation.

Conclusion: Remifentanil showed a more stable hemodynamic response during the surgery compared with the use of alfentanil in anesthetized patients undergoing laparoscopic cholecystectomy using TIVA. Both opioids, alfentanil and remifentanil, have a similar recovery profile, and they do not delay time to awakening.

Key words: Alfentanil, laparoscopic cholecystectomy, remifentanil, total intravenous anaesthesia

Introduction

Anesthetic techniques based on the use of high dose opioids offer hemodynamic stability and reduce intraoperative stress episodes.^[1] In addition, it reduces the hypnotic agent

requirements.^[2-4] However, most of the opioid accumulates in our body, causing adverse events such as respiratory depression or delay on the emergence of the anesthesia. This fact is also applicable for alfentanil, when infusion is prolonged in time (more than 2 h).

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Remifentanil is a potent ultra-short acting opioid analgesic, a specific mu-receptor agonist and 20 times more powerful than alfentanil.^[5] Its metabolism has an ester linkage which undergoes rapid hydrolysis by nonspecific tissue and plasma esterases,^[5,6] having a short terminal half-life (< 10 min)^[5,7] and a context-sensitive half-life at 4 min after a 4 h infusion.^[5,8,9] This means that the accumulation does not occur with remifentanil.

Contrary, alfentanil has a context-sensitive half-life at 50-55 min after a 3 h infusion and a terminal elimination half-life of 111 min.

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Remifentanil is not a substrate for plasma cholinesterase (pseudocholinesterase) and, therefore, in presence of atypical cholinesterase is expected a normal duration of action. Based on the metabolism of remifentanil, its pharmacodynamics is unaltered in patients with end-stage renal disease or severe hepatic dysfunction.^[10] However, in case of alfentanil this has to be taken into account since in presence of hepatic dysfunction its plasma half life is prolonged depending on cytochrome P450.^[3]

These two opioids have an appropriate pharmacological profile for outpatient laparoscopic procedures, due to the low incidence of nausea, vomiting, urinary retention, and postural hypotension. This fact allows discharge of patients from the hospital within a few hours after surgery.^[11]

Most of the studies performed to evaluate the use of total intravenous anesthesia (TIVA) are focused on the comparison between this technique and inhalational anesthesia for the prevention of postoperative nausea and vomiting after surgery. Few authors have studied TIVA for laparoscopy, and mostly in outpatient laparoscopic gynecological procedures.^[11-13] Therefore, we conducted this study to compare the suppression of intraoperative responses and recovery profiles between remifentanil and alfentanil in laparoscopic cholecystectomy.

Material and Methods

This randomized prospective study was approved by Local Research Ethics Committee of the Hospital Sur on 10 May 2013. Written informed consent was obtained from all participants and recruitment ended on 30 May 2014. We prospectively randomized 100 adult patients scheduled for elective laparoscopic cholecystectomy. Patients were excluded if they presented American Society of Anesthesiologists physical status 4, uncontrolled hypertension, electrocardiogram (ECG) identification of arrhythmias, previous history of alcohol or drugs abuse, pregnant/breastfeeding women, and patients using opioid medications for 12 h prior to surgery.

Patients were randomly assigned using computer generated random numbers to one of the two groups to be managed with either remifentanil (group R) or alfentanil (group A).

Patients were premedicated with midazolam 0.03 mg/kg intravenously, and standard anesthetic monitoring was attached (ECG, bispectral index, noninvasive blood pressure, pulse oximetry, and capnography). Anesthesia was performed by two senior anesthesiologists experienced in opioid drug and TIVA techniques.

Prior to the induction all patients underwent preoxygenation with a face mask and anesthesia was induced with intravenous remifentanil 0.4 µg/kg/min or alfentanil 10 µg/kg/min, with a target controlled infusion (TCI) propofol concentration of 4-6 µg/mL and cisatracurium 0.15 mg/kg. After optimum conditions for intubation had been achieved (relaxation of the jaw, loss of eyelash reflex and onset of apnea), endotracheal intubation was performed.

Anesthesia was maintained with TCI propofol concentration of 2.5 µg/mL, cisatracurium 1.5 µg/kg/min in 50% oxygen and air using volume controlled ventilation. Neuromuscular blockade was monitored to maintain a train-of-four of 2 twitches. Ventilatory parameters were monitored continuously and adapted to give a SpO₂ >95% and EtCO₂ 35-45 mmHg.

Once surgical procedure was initiated, opioid continuous infusion was set as follows: Remifentanil 0.25 µg/kg/min and alfentanil 5 µg/kg/min, respectively. TCI propofol infusion was stopped 5 min before the end of surgery, alfentanil and cisatracurium infusions 10 min before the end of the procedure and remifentanil was stopped at skin wound closure.

Residual effects of neuromuscular blocking were reversed using 2.5 mg neostigmine and 1 mg atropine.

We observed the patient's response to intubation, to first surgical incision and over the surgical procedure. We defined different kind of response to these events: Somatic responses (shivering, movements, and eye opening), autonomic responses (sweating and tears), hypertensive responses (systolic blood pressure > 15 mmHg over basal value for at least 1 min) and tachycardic responses (> 10 heart rates over basal value for at least 1 min).

If any of these responses happened, we doubled opioid infusion rate during 3 min, if the response was not controlled after that, we doubled again opioid infusion rate. When the response was not controlled under these conditions, then we increased TCI propofol infusion by 0.5 µg/mL increments as needed to control the response. Once the event was controlled, we returned to normal infusion rates.

In case of hypotension (systolic blood pressure < 80 mmHg for at least 1 min), we increased fluid flow rate administration, if it was not effective enough, then propofol infusion was decrease in 0.25 µg/mL reductions. Drugs infusions were reduced when necessary and additionally we used ephedrine or other vasopressor drugs if necessary.

We provided 2 µg/kg fentanyl and 50 mg dexketoprofen 10 min before the end of surgery. They received 1 mg/kg tramadol in the case of pain during their stay in PACU.

All patients received 4 mg ondansetron during the anesthetic procedure in order to prevent nausea or vomiting.

During the emergence from anesthesia, we recorded some variables regarding awakening of patients in both groups: Time to the first spontaneous breathing, time to successful ventilation, time to respond to verbal orders, and time to extubation.

An observer anesthesiologist who measured times and events was blinded to the type of opioid used (he was watching multiparameter monitor, which was turned in order to impede this observer to see how the anesthesiologist handled drugs), as well as the surgeon who performed the laparoscopic procedure (a high screen bar was placed to separate the surgeon field from the anesthesia field using a surgical drape).

Statistical analysis

We calculated sample size to detect a clinically significant difference of 10% in the number of events of one or more responses during the surgical procedure between the groups with 85% power ($1 - \beta = 0.85$) and a significance level of 0.05 (two-tailed), as 44 patients per group. A total of 104 patients were recruited to account for a 12% dropout rate.

Patient's responses during the surgical procedure needing increase in opioid infusion rate, responses to intubation and to first surgical incision were analyzed using a logistic regression model. The number of responses during the surgical procedure and the number of hypotensive episodes were analyzed by the Cochran-Mantel-Haenszel test. Recovery times were analyzed using a Cox proportional hazards regression model.

We analyzed the data with SPSS version 17 (SPSS Inc., Chicago, Illinois, USA).

Statistical analysis was performed with two-tailed tests, and a $P < 0.05$ was considered significant.

Results

We recruited 104 patients, and excluded 4 patients after randomization because the surgical approach changed from laparoscopy to open surgery. The results of 100 patients (50 remifentanyl and 50 alfentanil) were finally analyzed. The groups were comparable for demographic and surgical data [Table 1].

The number of responses to intubation and responses to first surgical incision were significantly lower in the R group compared with A group (14% vs. 30%; $P = 0.013$ and 8% vs. 18%; $P = 0.037$, respectively).

The event of one or more responses during the surgical procedure was also lower in the R group with respect to the A group (56% vs. 70%; $P = 0.017$) [Table 2].

The alfentanil group reported a larger number of responses during surgery than the remifentanyl one: Group A (19 patients had between 1 and 2 responses, 13 patients between 3 and 5 responses and 3 patient between 5 and 6 responses) and group R (17 patients had between 1 and 2 responses, 9 patients between 3 and 5 responses and 1 patient between 5 and 6 responses).

We observed that the hypertensive events during the procedure was lower in the R group as well as a lower frequency of tachycardia episodes in this group (34% vs. 56%; $P = 0.033$ and 28% vs. 44%; $P = 0.041$, respectively).

No differences were found between groups relating the percentage of hypotensive episodes (21% for remifentanyl and 19% for alfentanil). No episodes of bradycardia were seen.

There were no differences relating to recovery times (time to the first spontaneous breathing, time to successful ventilation, time to respond to verbal orders, and time to extubation) between the groups [Table 2].

No postoperative adverse episodes of nausea, vomiting, apnea, muscle rigidity or ventilatory depression were reported for both groups.

Discussion

The main goal of this study was the comparison between the use of remifentanyl and alfentanil regarding hemodynamic stability and recovery times from anesthesia in patients

Table 1: Demographic and surgical data

Variables	Remifentanyl	Alfentanil	P
Sex (female/male)	28/22	24/26	0.98
Age (year)	58±12	56±15	0.94
Weight (kg)	72.5±13.6	73±12.3	0.60
Height (cm)	165±8.5	164±8.4	0.12
BMI (kg/m ²)	26.6±3.2	27.2±3.6	0.84
ASA 1/2/3	11/23/16	9/25/16	0.75
Surgical time (min)	72±20	70.2±28	0.47
Peritoneal insufflation time (min)	56±18	55.5±25	0.15

Values are presented as mean±SD or numbers. SD = Standard deviation, BMI = Body mass index, ASA = American society of anesthesiologists

Table 2: Response to stimuli and recovery time data

Variables	Remifentanil	Alfentanil	P
Response to stimuli			
Response to tracheal intubation (n, [%])	7 (14)	15 (30)	0.013*
Response to first surgical incision (n, [%])	4 (8)	9 (18)	0.037*
Response during surgical procedure (n, [%])	27 (56)	35 (70)	0.017*
Hypertensive response during surgical procedure (n, [%])	17 (34)	28 (56)	0.033*
Tachycardia episode during surgical procedure (n, [%])	28	44	0.041*
Recovery time			
Time to first spontaneous breathing (min)	4±3	5±2	0.670
Time to successful ventilation (min)	6±2	7±4	0.770
Time to respond to verbal orders (min)	7±3	8±3	0.654
Time to extubation (min)	10±4	10±3	0.998

*P < 0.05. Values are presented as mean ± SD, numbers or percentage. SD = Standard deviation

undergoing laparoscopic cholecystectomy procedure using a TIVA technique.

The remifentanil infusion dose used in our study was based on previous clinical trials,^[11,12] and alfentanil infusion dose was based on our previous clinical experience, resulting in an equipotent remifentanil dose. Contrary to the dose used in previous studies, our dose was 5 times larger.^[12,14] In spite of this fact, time to recovery was not prolonged if the drug infusion was stopped 10 min before the end of the surgery, also these were relatively short surgical procedures and there was no accumulation of the drug.

Intubation and surgical incision are both potent stimuli that need an adequate analgesic level. Due to this fact, we used double dose of the analgesic infusions during this period. However, in spite of this measure, we observed hemodynamic responses in both groups, but the number of responses to intubation and responses to first surgical incision were significantly lower in the R group. It might be possible to use even larger doses of alfentanil to mitigate this effect without causing a delay on the recovery time.

Remifentanil infusion has been proved to reduce the hypnotic drugs requirements, like propofol used in our study, in order to maintain an adequate depth of anesthesia during a TIVA technique.^[4]

We also observed that the hemodynamic response to surgical stimuli was better controlled in the R group as well as a lower frequency of hypertension and tachycardia episodes in this group, as shown by other authors.^[12] Our results are comparable to Demirbilek *et al.* study, as they found that remifentanil provided better hemodynamic stability than alfentanil during anesthesia. However, these authors found that both remifentanil and alfentanil had similar effects on the stress endocrine response (including cortisol, insulin and glucose) to abdominal hysterectomy.^[15]

Other work conducted by Nilsson *et al.*, concluded that patients receiving remifentanil showed no stress responses (hypertension, tachycardia, somatic or autonomic responses) compared to the alfentanil group, and it was statistically significant. Although, more patients in the remifentanil group experienced hypotension or bradycardia requiring intervention than in the alfentanil group.^[16]

Previous works reported the association between prolonged administration of alfentanil and a longer terminal elimination half-life.^[17] In order to balance this fact out, the infusion of alfentanil was interrupted 10 min before the end of the surgery. In our study, this was enough to obtain a similar recovery times (including time to extubation) between the groups. We did not find differences in the recovery profile between opioids studied and our results are consistent with other studies concluding that remifentanil and alfentanil provided a reasonably rapid and reliable recovery. Remifentanil-based TIVA was associated with high intraoperative cost and early postoperative pain, but it allowed a more rapid respiratory recovery.^[18]

More recently, another group, led by Entezarias, reported no differences on recovery time between alfentanil and remifentanil groups in the anesthesia for surgical treatment of the elderly.^[19]

Other studies similar to ours, reported some muscle rigidity episodes during induction using both remifentanil and alfentanil,^[12,14] but it did not happen in our study, probably because we did not use bolus injections of these opioids and due to the preventive effect of cisatracurium.

When propofol-based TIVA is used for surgery, short-acting opioids as remifentanil and alfentanil do not significantly affect the risk of PONV. In this sense, our results are similar to other studies.^[20] However, other authors found differences between these opioids and concluded that patients anesthetized

with remifentanil have less postoperative nausea than with alfentanil.^[13] This last work, performed by Rognås and Elkjaer is the only study that we found comparing these two opioids in laparoscopy, and it was a large comparison of 861 females undergoing day case laparoscopic sterilization under general anesthesia using the TIVA technique.^[13] Contrary, the incidence of nausea and vomiting in the remifentanil group was significantly higher than alfentanil group in a comparison evaluating the effects of these drugs in elderly patients.^[19]

Our study has a number of limitations. First, the anesthesiologist who performed anesthesia was not blinded to the type of opioid. Postoperative outcome assessors were blinded to the group assignment in order to mitigate that limitation. Second, noninvasive blood pressure was monitored, so it was not as reliable as invasive blood pressure monitoring in order to detect hypertensive response to stimuli.

Conclusion

We conclude that in this randomized study, remifentanil administered as a continuous infusion 0.5 µg/kg/min during the induction, tracheal intubation, and first surgical incision, followed by a 0.25 µg/kg/min dose for the rest of the surgical procedure, combined with a TCI propofol concentration of 2.5 µg/mL, showed a more stable hemodynamic response during surgery compared with the use of continuous infusion of alfentanil 10 µg/kg/min and 5 µg/kg/min, respectively, in anesthetized patients undergoing laparoscopic cholecystectomy. Based on our results, we can conclude that regardless of the kind of opioid used (alfentanil or remifentanil), recovery profile was similar and time to awakening was not delayed.

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