Effect of timing of morphine administration during remifentanil-based anaesthesia on early recovery from anaesthesia and postoperative pain

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Background. Since the time to peak analgesic effect of intravenous morphine can be longer than 40–60 min in volunteers, the goal of this study was to evaluate the effect of the timing of intraoperative morphine administration on early postoperative pain.

Methods. A total of 120 adult patients undergoing laparoscopic cholecystectomy were studied. Anaesthesia was induced with remifentanil and etomidate and maintained with remifentanil and sevoflurane/nitrous oxide. Morphine 150 µg kg^{-1} was given randomly at three different times during surgery, and a fourth group received placebo. Times to eyes opening and extubation were measured, and pain was evaluated in the post-anaesthesia care unit (PACU) using a visual analogue scale (VAS). Morphine 2–3 mg was given when the VAS score was ≥50 mm. The four groups were, according to the time elapsed from morphine administration to the end of surgery, group 1 (*n*=30): placebo; group 2 (*n*=33): <20 min; group 3 (*n*=30): 20–40 min; group 4 (*n*=27): >40 min.

Results. Recovery from anaesthesia and pain scores were similar in all groups. However, mean (SD) morphine consumption was 5.7 (4.7) mg in group 1, 4.4 (4.2) mg in group 2, 4.7 (4.7) mg in group 3, and 2.2 (4.0) mg in group 4 (*P*<0.05, group 1 *vs* 4). Morphine was required in only 38% of patients in group 4 compared with 83%, 67% and 69% in groups 1, 2, and 3, respectively (*P*<0.01, group 1 *vs* 4).

Conclusions. The timing of intraoperative morphine administration did not affect the early recovery from anaesthesia. However, the reduction in the number of patients requiring morphine in the PACU when morphine had been given more than 40 min before the end of surgery supports this practice, rather than administration closer to the end of surgery.

The pharmacokinetic characteristics of remifentanil, particularly the short context-sensitive half-time, allow anaesthetic techniques based on high plasma concentrations of this opioid, with fast recovery at the cessation of its infusion.[1] However, this characteristic can, in turn, become a disadvantage at the end of anaesthesia as the rapid offset of the effects of remifentanil can result in early and severe postoperative pain if the analgesic regimen has not started during surgery.[2] Different schemes for postoperative pain management have been proposed, including the continuation of remifentanil infusion, regional or local blocks and the administration of longer-acting opioids during surgery.[2]

When using this last approach, a common practice is to administer morphine 20–30 min before the end of surgery.[3–7] However, experimental evidence in humans shows that the time to peak analgesic effect of this drug can be longer than 40 min.[8 9] Thus, there may be insufficient time for morphine to reach the maximum analgesic activity before the effect of remifentanil disappears. In addition, if morphine is given close to the end of surgery, its sedative effects might delay recovery from anaesthesia; this potential adverse effect has not been studied.

In this study, we have evaluated the effect of the timing of intraoperative morphine administration on the early

recovery from anaesthesia and on pain scores and morphine consumption after laparoscopic cholecystectomy under remifentanil-based anaesthesia in adults.

Materials and methods

After obtaining Institutional Ethics Committee approval and informed consent, 120 unpremedicated patients, aged 20–60 yr, ASA I or II, scheduled for elective laparoscopic cholecystectomy under general anaesthesia were studied. Exclusion criteria included chronic or acute (within the last 48 h) intake of any sedative or analgesic drug, and any known adverse reaction to the study drugs.

In the operating room, routine monitoring of arterial pressure, electrocardiogram, and pulse oximetry was initiated. Remifentanil was started at 0.3 μg kg^{-1} min^{-1} and patients were preoxygenated with 100% oxygen. After 5 min the remifentanil infusion was increased to 0.5 μg kg^{-1} min^{-1} and etomidate 0.2–0.3 mg kg^{-1} was injected. Tracheal intubation was facilitated with rocuronium 0.4–0.6 mg kg^{-1}, and patient's lungs were ventilated mechanically to maintain the end-tidal CO_2 at 4.0–4.7 kPa. Maintenance of anaesthesia was with 1% end-tidal concentration of sevoflurane in 50% nitrous oxide, and the remifentanil infusion rate was adjusted to maintain arterial pressure within 20% of the value measured on the ward. The total amount of remifentanil administered and the final infusion rate immediately before discontinuing anaesthesia were recorded. No prophylactic antiemetic drugs were given.

After induction of anaesthesia, all patients received ketorolac 60 mg i.v. and were assigned, by means of random numbers, to one of four groups ($n=30$ each) to receive saline or morphine 150 μg kg^{-1} i.v. at one of three points during surgery: beginning of surgery, clipping of the cystic artery, or during skin closure. Three 10 ml syringes were prepared for each patient, containing only saline (placebo group), or morphine in one syringe and saline in the other two. According to randomization, these syringes were labelled 1–3 and the contents administered in sequence at the three surgical stages by a blinded investigator.

During skin closure, neuromuscular blockade was evaluated and antagonized with neostigmine and atropine when necessary. At the last skin suture, the remifentanil infusion and anaesthetic gases were discontinued (T_0). Patients remained on mechanical ventilation with the same ventilatory parameters and 100% oxygen (5 litre min^{-1}) for a further 90 s and then were not ventilated until spontaneous breathing occurred. No stimulation was applied to patients during this period, and extubation was performed when the patient rejected the tracheal tube.

All measurements were made by investigators blinded for the study drugs. Evaluation of early recovery from anaesthesia was by the time to extubation (time from T_0 to extubation) and time to eyes opening (time from T_0 to spontaneous eye opening). In the post-anaesthesia care unit (PACU) patients breathed room air. Evaluations included ventilatory frequency, continuous Sp_{O_2}, degree of sedation (0 = awake, 1 = drowsy, 2 = asleep, but could be wakened, 3 = deep sleep, difficult to wake up), pain scores both at rest and on coughing using a visual analogue scale (0 mm, no pain to 100 mm, unbearable pain), and emetic episodes. All measurements were recorded on arrival, every 15 min for 60 min, and thereafter every 30 min until discharge to the ward. Morphine 2–3 mg i.v. was given every time the pain score at rest was $\geqslant$50 mm. In case of retching, vomiting, or nausea lasting longer than 15 min, ondansetron 4 mg i.v. was administered. Hypoxaemia ($Sp_{O_2}<90\%$) was treated with 40% oxygen by mask. Discharge of patients from the PACU was at the discretion of the attending anaesthetist and no attempt was made to speed up this process.

Data analysis

From our experience and previous studies,[3 4] more than two-thirds of patients undergoing this or similar surgery under remifentanil-based anaesthesia plus intraoperative morphine require additional morphine in the PACU. Power analysis was calculated to find as statistically significant a reduction from 70% to 35% in patients requiring morphine with $\alpha=0.05$ and $\beta=0.20$, resulting in a sample size of 29 patients per group. Because of the usual variability in the duration of surgery, four groups were defined according to the time elapsed from morphine administration to the end of surgery: group 1 ($n=30$) control or placebo; group 2 ($n=33$) <20 min; group 3 ($n=30$) 20–40 min; group 4 ($n=27$) >40 min. Statistical analysis was with one-way ANOVA for general data, times for evaluation of recovery from anaesthesia and amount of morphine administered in the PACU. Pain scores were analysed with two-way ANOVA. Continuous variables with non-normal distribution (times to reach a given degree of sedation and to the first dose of morphine in the PACU) were analysed using the Kruskal–Wallis test. The number of patients requiring morphine, incidence of hypoxaemia, and postoperative emesis were analysed with the chi-squared test. Bonferroni's correction was used for multiple comparisons. $P<0.05$ was considered significant. Generation of the table of random numbers and all calculations were performed with StatView SE+Graphics v1.04 (Abacus Concepts, Inc., CA, USA). Values are mean (SD) unless otherwise stated.

Results

There were no significant differences between groups in patient characteristics, duration of surgery or anaesthesia, and mean infusion rate of remifentanil (Table 1). Time from morphine injection to the end of surgery was 8.0 (4.2) min in group 2, 30.4 (5.3) min in group 3, and 60.3 (16.7) min in group 4 ($P<0.0001$). Approximately one-third of patients in each group required neostigmine at the end of surgery.

Indices of early recovery from anaesthesia were similar in the four groups (Table 2). In the PACU, one patient in group

Table 1 Patient characteristics. [†]The remifentanil infusion rate was calculated from the total amount given, weight of the patient, and duration of anaesthesia. Values are mean (SD or range). No significant differences were found between groups

	Group 1	Group 2	Group 3	Group 4
Age range (yr)	42 (20–58)	42 (25–60)	41 (21–60)	42 (23–57)
Weight (kg)	69 (13)	69 (16)	75 (15)	70 (13)
Height (cm)	163 (9)	164 (9)	166 (9)	164 (10)
Male/female	10/20	9/24	10/20	11/16
ASA I/II	24/6	23/10	22/8	20/7
Duration of anaesthesia (min)	73 (17)	75 (23)	71 (20)	82 (20)
Duration of surgery (min)	54 (17)	56 (22)	50 (17)	60 (18)
Remifentanil (μg kg^{-1} min^{-1})[†]	0.26 (0.05)	0.28 (0.06)	0.25 (0.06)	0.27 (0.04)
Final infusion rate of remifentanil (μg kg^{-1} min^{-1})	0.13 (0.08)	0.13 (0.09)	0.12 (0.08)	0.12 (0.07)
Intraoperative crystalloids (ml)	852 (222)	938 (212)	872 (174)	838 (165)

Table 2 Early recovery from anaesthesia. Values are mean (SD) [range]. No significant differences were found between groups

	Group 1	Group 2	Group 3	Group 4
Time to extubation (min)	7.0 (3.8) [0.7–14.3]	9.3 (4.9) (1.0–26.0)	9.1 (4.3) (3.3–19.0)	9.6 (4.2) [2.8–19.0]
Time to eyes opening (min)	7.0 (4.1) [0.7–16.8]	9.2 (5.2) [1.0–26.0]	8.9 (4.7) [1.9–22.0]	9.6 (4.3) [2.5–19.0]

3 and one in group 4 were lost from follow up. No patient arrived at the PACU with a sedation grade of 3 or more, and median time (range) to reach grade 0 was: 0 (0–60) min in group 1, 30 (0–150) min in group 2, 0 (0–120) min in group 3 and 0 (0–120) in group 4 (not significant). Four patients in groups 1 and 2 and one patient in group 3 were sent to the ward with a sedation grade of 1.

No significant differences were found in pain scores either at rest or on coughing (Figs 1 and 2). Median times (range) to morphine administration were 0 (0–60) min in group 1, 0 (0–45) min in group 2, 0 (0–45) min in group 3, and 30 (0–60) in group 4 (not significant). Mean morphine consumption was 5.7 (4.7) mg in group 1, 4.4 (4.2) mg in group 2, 4.7 (4.7) mg in group 3, and 2.2 (4.0) mg in group 4 ($P<0.05$ with one-way ANOVA; $P<0.05$ group 1 *vs* group 4 with unpaired Student's *t* test and Bonferroni's correction). Morphine was required in 83% of patients in group 1, 67% in group 2, 69% in group 3, and 38% in group 4 ($P<0.01$ with all groups and for group 1 *vs* group 4).

Hypoxaemia occurred in 7% of patients in group 1, 15% in group 2, 24% in group 3, and 0% in group 4 ($P<0.05$). All episodes were successfully treated with 40% oxygen by mask. No patient had a ventilatory frequency <12 bpm.

The incidence of postoperative emesis (95% confidence interval) was 47% (29–65%) in group 1, 73% (58–88%) in group 2, 66% (49–83%) in group 3, and 62% (44–80%) in group 4 (not significant).

Mean time to discharge to the ward was: 111 (28) min in group 1, 117 (30) min in group 2, 120 (47) min in group 3, and 110 (31) in group 4 (not significant).

Discussion

The main findings of this study are that, during remifentanil-based anaesthesia, the timing of intraoperative morphine administration does not significantly affect early recovery
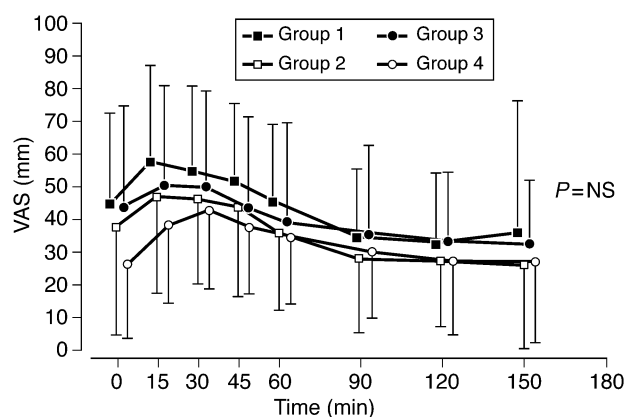
Fig 1 Pain scores at rest in the four groups during the stay in the PACU. No significant differences were found among groups with two-way ANOVA. VAS, visual analogue scale.
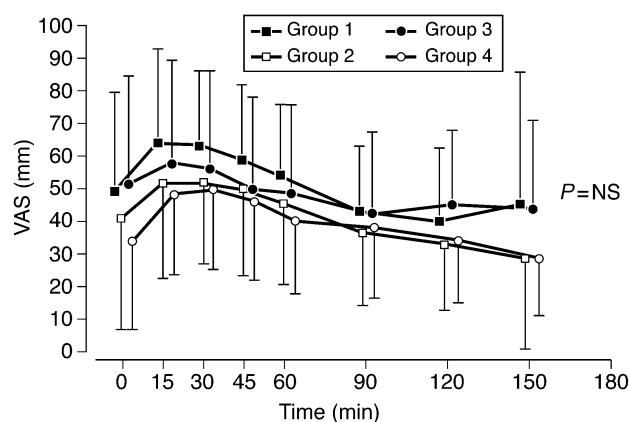
Fig 2 Pain scores on coughing in the four groups during the stay in the PACU. No significant differences were found among groups with two-way ANOVA. VAS, visual analogue scale.

from anaesthesia. However, only the administration of morphine more than 40 min before the end of surgery resulted in fewer patients requiring morphine in the PACU compared with the placebo group.

The rapid offset of action of remifentanil on discontinuation of infusion has resulted in new challenges in postoperative pain management, especially when this opioid is the main analgesic component for major surgery.[2] Basically, two strategies are used to deal with this problem: either the intraoperative analgesic infusion (i.e. remifentanil) is continued at a reduced rate in the postoperative period[3 10 11] or the postoperative analgesic regimen is started during surgery.[3] Although postoperative remifentanil infusion can be effective for pain management, the high incidence of respiratory depression,[10] need for close monitoring by an anaesthetist,[3 11] requirements of additional equipment for infusion in the PACU, and the fact that this technique can only postpone the initiation of definitive pain management, thus leading to longer stays in the PACU,[3] have resulted in a more widespread use of the second approach, including regional blocks and intraoperative opioid administration.[3 7]

Morphine is one of the most commonly used drugs for pain control after surgery under remifentanil-based anaesthesia, and in most studies that start its administration intraoperatively, morphine is given 20–30 min before the anticipated end of surgery.[3 7] Since evidence from human volunteers suggests that the time to maximal analgesic activity of morphine can be longer than 40 min,[8 9] this study aimed to evaluate whether the timing of intraoperative morphine administration, in particular its administration more than 40 min before the end of surgery, can result in better early postoperative pain control. We found that the only group showing a reduced morphine consumption compared with patients given placebo was the group that received morphine more than 40 min before the end of surgery. In addition, only 38% of patients in this group required morphine, compared with two-thirds in groups 2 and 3, and more than 80% in the control group. Although pain scores were similar between groups, in groups 1–3 this was at the cost of aggressive initial pain management and more time spent by nurses administering morphine. In addition, with this protocol, every patient who received morphine represents a patient with moderate to severe pain. Thus, we believe that the 50% reduction in the number of patients requiring morphine in the PACU in group 4 is clinically useful. However, more studies are needed to evaluate whether these results last beyond the early postoperative period and improve outcome.

While a better matching between the time of morphine administration and its peak analgesic effect at the moment of arrival at the PACU in group 4 could explain our results, a pre-emptive analgesic effect of morphine in these patients is theoretically possible. Although the clinical effectiveness of pre-emptive analgesia is controversial,[12 13] i.v. morphine administered at induction of anaesthesia reduced the morphine consumption within the first 24 h after hysterectomy compared with patients who received morphine at closure of the peritoneum.[14] Classical pre-emptive interventions start the analgesic regimen before the surgical incision,[12 13] and our patients in group 4 received morphine at the moment of the Verres needle insertion. However, if the analgesic drug is administered before high-intensity noxious stimulation that occurs later in the surgery, a pre-emptive analgesic effect is still possible.[13] Although the possibility of a pre-emptive effect of morphine given during the administration of clinically useful infusion rates of remifentanil can be low, strictly speaking it cannot be ruled out on the basis of the results of this study.

In addition to a submaximal analgesic effect when morphine is administered close to the end of surgery, some adverse effects, such as sedation, might be more marked. However, we found no differences in any of the indices of early recovery from anaesthesia or degree of sedation in the PACU. It is possible that morphine 0.15 mg kg^{-1} does not produce sufficient sedation to significantly prolong recovery of anaesthesia as evaluated in this study. In agreement with this possibility, Katoh and Kimura found that morphine 0.1 mg kg^{-1} does not affect the concentration of sevoflurane at awakening.[15] Hypoxaemia (Sp_{O_2}<90%) occurred in no patient in group 4 compared with 15% and 24% of patients in groups 2 and 3, respectively. All these episodes occurred while patients were breathing room air; no case was associated with a ventilatory frequency lower than 12 bpm, and all responded to 40% oxygen by mask. This incidence of hypoxemia appears similar to that reported by others. Fletcher and colleagues found that respiratory side-effects (defined as apnoea, hypoxia, or respiratory depression requiring naloxone or mechanical ventilation) occurred in 2% and 8% of patients receiving morphine 0.15 and 0.25 mg kg^{-1}, respectively, 30 min before the end of surgery.[7] The study by Albrecht and colleagues found that one out of 20 patients given morphine 15 mg had transient hypoxemia that resolved spontaneously,[5] and Yarmush and colleagues found that no patient given morphine 0.15 mg kg^{-1} showed a ventilatory frequency <8 bpm.[3] While comparisons between these studies are not possible because of the different definitions of respiratory depression, it seems that severe postoperative respiratory depression is not frequent with the dose of morphine utilized in our study, especially when morphine is given more than 40 min before the end of surgery.

Overall, two-thirds of patients receiving intraoperative morphine complained of postoperative nausea and vomiting in the PACU, possibly secondary to the combination of etomidate, remifentanil and morphine. A possible relationship between morphine given in the PACU and episodes of emesis and hypoxaemia was not confirmed by a *post hoc* analysis.

In conclusion, in adults undergoing laparoscopic cholecystectomy under a remifentanil-based anaesthesia, intra-

operative administration of morphine for postoperative pain management does not prolong early recovery from anaesthesia. However, administration of morphine more than 40 min before the end of surgery has the advantage of reducing by almost 50% the number of patients requiring a second dose in the PACU compared with those who received morphine closer to the end of surgery.

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