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A comparison of anaesthesia using remifentanil combined with either isoflurane, enflurane or propofol in patients undergoing gynaecological laparoscopy, varicose vein or arthroscopic surgery

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Background: Anaesthesia comprising remifentanil plus isoflurane, enflurane or propofol was randomly evaluated in 285, 285 and 284 patients, respectively, undergoing short-procedure surgery.
Methods: Anaesthesia was induced with propofol (0.5 $mg \cdot kg^{-1}$ and 10 $mg \cdot 10\ s^{-1}$), and a remifentanil bolus (1 $\mu g \cdot kg^{-1}$) and infusion at 0.5 $\mu g \cdot g^{-1} \cdot min^{-1}$. Five minutes after intubation, remifentanil infusion was halved and 0.5 MAC of isoflurane or enflurane, or propofol at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were started and titrated for maintenance.
Results: Patient demography and anaesthesia duration were similar between the groups. Surgery was performed as daycases (52%) or inpatients (48%). The median times (5–7 min) to extubation and postoperative recovery were similar between the groups. Responses to tracheal intubation (15% vs 8%) and skin incision (13% vs 7%) were significantly greater in the total intravenous anaesthesia (TIVA) group ($P<0.05$). Fewer patients given remifentanil and isoflurane (21%) or enflurane (19%) experienced ≥1 intraoperative stress response compared to the TIVA group (28%) ($P<0.05$). Median times to qualification for and actual recovery room discharge were 0.5–0.6 h and 1.1–1.2 h, respectively. The most common remifentanil-related symptoms were muscle rigidity (6–7%) at induction, hypotension (3–5%) and bradycardia (1–4%) intraoperatively and, shivering (6–7%), nausea and vomiting postoperatively. Nausea (7%) and vomiting (3%) were significantly lower with TIVA compared with inhaled anaesthetic groups (14–15% and 6–8%, respectively; $P<0.05$).
Conclusion: Anaesthesia combining remifentanil with volatile hypnotics or TIVA with propofol was effective and well tolerated. Times of extubation, postanaesthesia recovery and recovery room discharge were rapid, consistent and similar for all three regimens.

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Key words: Anesthesia; outpatient; inpatient; volatile; isoflurane; enflurane; TIVA; propofol; μ-opioid receptor agonist; remifentanil; recovery.

REMIFENTANIL is a highly potent, selective μ-opioid receptor agonist, belonging to the class of 4-anilidopiperidine derivatives. It is rapidly metabolised by non-specific esterases to remifentanil acid that is about 4600 times less potent (1, 2). The terminal plasma half-life of remifentanil is 8–10 min and its context sensitivity, i.e. biological half-life, is 3–5 min regardless of the duration of infusion. These characteristics should offer advantages in clinical practice compared with other opioids (1, 3–6).

Remifentanil, like other opioids, reduces isoflurane and propofol requirement (7, 11, 12). Although the clinical potential of remifentanil to reduce enflurane requirements has not been investigated, animal studies have demonstrated that opioids of the same class, i.e. alfentanil, sufentanil or fentanyl, can reduce the minimal alveolar concentration (MAC) requirement of enflurane (7–10).

Most remifentanil investigations have involved comparisons with other opioids during anaesthesia. This study was undertaken to evaluate the efficacy and tolerability of anaesthetic techniques comprising remifentanil with the inhaled agents isoflurane or enflurane versus total intravenous anaesthesia (TIVA) with remifentanil and propofol for short procedure surgery performed either on daycase or inpatient basis.

Methods

The study comprising two, identical, open, randomised, multicentre protocols (USAB3117 and USAB3123) recruited 854 patients from 70 centres across Canada, New Zealand, South Africa and 11 European countries. The study was approved by the individual Institutional Ethics Committee and by the participating country's regulatory authority if appropriate. All patients gave signed informed consent.

Patients aged ≥18 yr, of ASA status 1–3, undergoing elective gynaecological laparoscopy, varicose vein or arthroscopic surgery anticipated to last 30 min or longer were eligible. Patients were excluded if they showed significant arrhythmia, uncontrolled hypertension (diastolic blood pressure ≥100 mmHg), severe or uncontrolled disease, weight 100% greater than ideal body weight, hypersensitivity to opioids and chronic use of opioids, benzodiazepines, anticonvulsants, clonidine or alpha-2-adrenoceptor agonists or the use of these drugs within 12 h prior to surgery (except for overnight sedation with a short-acting benzodiazepine). Pregnant and lactating women were also excluded. Women of childbearing potential were entered only if they had a negative pregnancy test on the study day. Patients in whom the use of nonsteroidal anti-inflammatory drugs (NSAIDs) was contraindicated were excluded. No premedication was allowed. Patients were randomised to anaesthesia comprising remifentanil with isoflurane, enflurane or propofol using a computer-generated random code that ensured equal allocation of the study treatments at each centre.

Before induction, patients received 5 $ml \cdot kg^{-1}$ intravenous loading (e.g. Ringer's) followed by glycopyrrolate (0.1–0.2 mg) or atropine (0.4–1.0 mg) and breathed 100% oxygen for 3 min. At induction, remifentanil was given as an initial slow bolus of 1 $\mu g \cdot kg^{-1}$ (over 30–60 s) followed immediately by a continuous infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; propofol was administered for induction at 0.5 $mg \cdot kg^{-1}$ followed by 10 mg every 10 s to loss of consciousness (LOC). For patients randomised to remifentanil and propofol, an infusion of propofol was started at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If required, any diminution in LOC prior to laryngoscopy or tracheal intubation was supplemented either with isoflurane or enflurane via a facemask (for the volatile anaesthetic groups) or with additional propofol boluses for the TIVA group. Muscle relaxation was achieved with a neuromuscular blocking agent of choice given at a dose level within the local prescribing recommendations. Five minutes after intubation the remifentanil infusion was reduced to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and titrated to per protocol requirement thereafter. Patients who received remifentanil plus the inhaled anaesthetic agent were ventilated with an initial end-tidal concentration of isoflurane of 0.6% (about 0.5 MAC) or an end-tidal concentration of enflurane of 0.9% (about 0.5 MAC) in an air/oxygen mixture. Patients receiving remifentanil plus propofol were ventilated with an oxygen/air mixture.

Responses to intubation, skin incision and intraoperative surgical stimuli were defined as one or more of the following:

- Hypertensive response: systolic blood pressure (SBP) >15 mmHg above preoperative baseline for ≥1 min.
- Tachycardic response: heart rate (HR) >90 beats per minute (bpm) for ≥1 min.
- Somatic response: gross movement, swallowing, grimacing, eye opening.
- Autonomic response: lachrymation, sweating.

Responses to surgical stimuli were monitored throughout and treated by the administration of one or more remifentanil bolus doses of 1 $\mu g \cdot kg^{-1}$ and/or by up to 100% increase in its infusion rate to a maximum of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If remifentanil failed to treat the response(s), isoflurane or enflurane was increased in incremental steps up to a maximum of 1 MAC and the propofol infusion increased stepwise to a maximum of 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If both of these failed, then 10–20 mg of propofol could be given to all treatment groups.

Hypotension (SBP<80 mmHg for ≥1 min) was managed firstly by intravenous fluid replacement followed by decreases in isoflurane, enflurane or the propofol infusion, or a decrease in the remifentanil infusion rate. Additional treatment of hypotension requiring vasopressor or anticholinergic drug(s) was classed as an adverse event. Bradycardia (HR <40 bpm for ≥1min) treated either with atropine or glycopyrrolate was classed as an adverse event.

For management of postoperative pain, patients received a non-opioid analgesic, e.g. NSAIDs, intraoperatively, and had the surgical incision(s) infiltrated with a local anaesthetic agent at closure. Residual neuromuscular blockade was reversed with neostigmine and glycopyrrolate or atropine. At the last suture, remifentanil was discontinued, as was isoflurane, enflurane or propofol administration. Upon resumption of spontaneous respiration and control of the airway, the trachea was extubated, and observations were continued in the recovery room. Any further analgesia required postoperatively was administered upon patient's demand and as per routine practice.

All recovery times were assessed from the cessation of the last maintenance anaesthetic agent, as were the times of qualification for and actual discharge from the recovery room and the hospital. For the sample size calculation, the logarithmically transformed values were assumed to have a standard deviation (SD) of 0.56 and an increase of 25% in the geometric means of time to extubation was considered clinically relevant. To achieve 90% power and to detect such a difference between each of the groups at the two-sided 5% level, a total of 133 per group per protocol was required. Secondary efficacy endpoints included: responses during tracheal intubation, skin incision and skin closure; incidence of intraoperative surgical stress response, hypotension and bradycardia; time to spontaneous respiration and adequate respiration (respiration rate $\geq$8 breaths per minute and/or end-tidal CO_2 ($PetCO_2$ $<$50 mmHg); time to response to verbal command; time to first Aldrete score $\geq$9 (13); time to eligibility for recovery room discharge (Aldrete score 9–10 and control of pain, nausea and vomiting) and actual discharge from recovery room to ward; time to qualification for discharge and actual discharge from hospital.

Safety was monitored by the recording of all adverse events occurring throughout the study and for up to 24 h after the end of anaesthesia. Muscle rigidity at induction, postoperative nausea or vomiting, intraoperative recall or postoperative shivering were also recorded as an adverse event.

Allocation of treatment randomisation to each investigator, protocol compliance and data management of the study was co-ordinated centrally. Patient demography and baseline characteristics in all three groups were summarised but no statistical comparisons made. The primary efficacy endpoint (time to extubation) was analysed using analysis of variance (14). The proportion of patients with at least one response to intubation and skin incision was analysed using logistic regression, and odds ratios and confidence intervals (CI) were calculated (15). The number of responses to surgical stress and the incidence of hypotension and bradycardia were analysed using the Mantel-Haenszel test (15). The time to recovery of respiratory function, time to response to verbal command, first Aldrete score $\geq$9 and discharge times from recovery room and from hospital were analysed using analysis of variance and Cox's proportional hazards regression; SBP and HR were analysed using analysis of covariance adjusted for baseline (16).

Results

A total of 854 patients was randomised to treatment: 285 patients received remifentanil-based anaesthesia with isoflurane, 285 patients with enflurane and 284

Table 1

Patient demography, ASA physical status, surgery type and duration of anaesthesia.

	Remifentanil +isoflurane	Remifentanil +enflurane	Remifentanil +propofol
Number of patients	285	285	284
Sex (male:female)	90:195	88:197	96:188
Age (mean, range; y)	37 (18–78)	38 (18–71)	37 (18–68)
Weight (mean±SD; kg)	69.3±13.2	70.9±14.4	71.7±14.2
Height (mean±SD; cm)	168±8.9	168±9.5	168±9.6
ASA physical status, N (%)			
ASA 1	243 (85%)	225 (79%)	247 (87%)
ASA 2	41 (14%)	56 (20%)	37 (13%)
ASA 3	1 (<1%)	4 (1%)	0
Surgery type, N (%)			
Gynaecological laparoscopy	135 (47%)	135 (47%)	135 (48%)
Varicose vein surgery	28 (0%)	18 (6%)	23 (8%)
Arthroscopic surgery	122 (43%)	132 (46%)	126 (44%)
Anaesthesia			
Duration (median, range; min)	53 (20–257)	53 (18–213)	52 (16–194)
Total remifentanil dose (mean±SD; μg/kg)	19.9 (9.4)	20.9 (11.2)	21.1 (11.5)
Case type, N (%)			
Inpatient	136 (48%)	136 (48%)	136 (48%)
Daycase	149 (52%)	149 (52%)	148 (52%)

* From beginning of first anaesthetic until end of last anaesthetic.

patients with propofol. Overall, the three treatment groups were similar with respect to demography, ASA physical status, surgery type, duration of anaesthesia, the total mean (SD) remifentanil dose ($\mu g \cdot kg^{-1}$) received and whether surgery was performed as daycase or inpatient (Table 1). The mean (SD) doses of propofol required to induce LOC were 1.4 (0.53), 1.4 (0.56) and 1.4 (0.53) $mg \cdot kg^{-1}$ for the isoflurane, enflurane and propofol anaesthesia groups, respectively. The overall mean (SD) end-tidal concentrations of isoflurane and enflurane were 0.72% (0.65) and 0.86 (0.21) respectively, whilst the mean (SD) infusion rate of propofol was 98.6 (17.2) $\mu g \cdot kg^{-1} \cdot min^{-1}$.

The study failed to demonstrate any differences between the anaesthesia groups in the times to extubation, which occurred within a median time of 7 min. Spontaneous respiration occurred within a median time of 5–6 min and adequate respiration within a median time of 7 min (Table 2). There were no differences between the treatment groups in the median times to an Aldrete score of ≥9, which ranged between 7 min and 9 min. However, the median time to respond to verbal command was found to be significantly longer (7 min) for the propofol treatment group compared with the isoflurane treatment group (6 min) (hazard ratio isoflurane to propofol, odds ratio 1.19; 95% CI, 1.01–1.41) ($P<0.05$).

A significantly greater number of patients receiving remifentanil with propofol (15%) responded to intubation compared with those receiving remifentanil with isoflurane (8%) (odds ratio 0.48; 95% CI, 0.27–0.83) ($P<0.01$) or enflurane (7%) (odds ratio 0.42; 95% CI, 0.23–0.74) ($P<0.05$) (Fig. 1). Similarly, significantly more patients in the propofol group experienced responses to skin incision (13%) than patients given isoflurane (7%) (odds ratio 0.45; 95% CI, 0.25–0.82) ($P<0.01$) or enflurane (8%) (odds ratio 0.47; 95% CI, 0.26–0.85) ($P<0.05$). There were no significant differences in response to skin closure between any of the three treatment groups: propofol (7%), isoflurane (5%) and enflurane (5%).

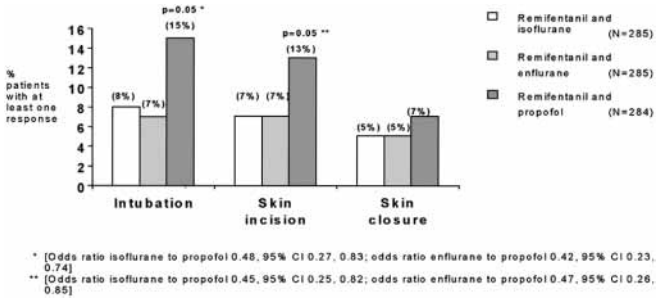

Fig. 1. Number of patients (%) with at least one response to intubation, skin incision and skin closure.

Significantly more patients in the propofol treatment group (28%) experienced at least one intraoperative response to surgical stress compared with those in the isoflurane (21%) or enflurane (19%) groups ($P<0.05$) (Table 3). In all three groups, the majority of the responses to surgical stress were hypertensive or tachycardic episodes. Sub-analysis showed that significantly more patients in the propofol group (10%) experienced a somatic response compared to patients in the isoflurane group (5%) ($P<0.05$). Similarly, significantly more patients in the propofol (18%) group experienced a hypertensive response than patients who had received enflurane (8%) ($P<0.05$). There were no differences between the three treatment groups in the incidence of intraoperative hypotension (6–7%) or in the incidence of bradycardia (<1–2%);

Table 2

Time to extubation, spontaneous and adequate respiration and, Aldrete score ≥9.

	Remifentanil +isoflurane (N=282)	Remifentanil +enflurane (N=285)	Remifentanil +propofol (N=282)
Time to spontaneous respiration (min)			
Median (Range)	5 (0–15)	5 (0–18)	6 (0–19)
Time to adequate respiration (min)			
Median (Range)	7 (1–30)	7 (1–20)	7 (1–20)
Time to extubation (min)			
Median (Range)	7 (1–20)	7 (1–20)	7 (1–20)
Time to response to verbal command (min)			
Median (Range)	6 (1–20)	6 (1–20)	7* (1–20)
Time to first Aldrete score ≥9 (min)			
Median (Range)	7 (1–49)	9 (1–45)	9 (1–50)

* (propofol to isoflurane $P<0.05$; Hazard ratio 1.19; 95% CI 1.01–1.41).

Table 3

Number (%) of patients with at least one response to intraoperative surgical stress.

	Remifentanil +isoflurane (N=285)	Remifentanil +enflurane (N=285)	Remifentanil +propofol (n=284)
*Intraoperative period	59 (21%)†	53 (19%)‡	80 (28%)
Hypertensive response	33 (12%)	24 (8%)	50 (18%)
Tachycardic response	26 (9%)	26 (9%)	26 (9%)
Somatic response	14 (5%)	21 (7%)	28 (10%)
Autonomic response	1 (<1%)	3 (1%)	3 (1%)

* Intraoperative=from skin incision to skin closure.
† Isoflurane to propofol $P<0.04$
‡ Enflurane to propofol $P<0.01$.

both were readily treatable with the anaesthetic agents used in the study.

The times for eligibility and actual discharge (from the recovery room or from the hospital) were similar across the three treatment groups (Table 4). In addition, data relating to eligibility for and actual discharge from the recovery room and the hospital were sub-analysed on the basis of whether the patient had been admitted for surgery as a daycase or an inpatient. Analysis for daycase patients also showed similarities between the three treatment groups in the eligibility for recovery room discharge (median time of 0.5–0.6 h) and in the times to actual discharge from the recovery room to the ward (median time of 1.2–1.3 h). For those patients admitted for surgery as inpatients, the respective median times for eligibility for recovery room discharge and actual times of discharge to the ward were 0.6 and 1.1 h, respectively, across all three treatment groups.

Daycase patients across all three treatment groups qualified for discharge from the hospital within 2.4–2.8 h after the end of anaesthesia. The median times to actual discharge for all three treatment groups were similar and ranged between 3.8 h and 4.1 h. Patients admitted as inpatients, however, qualified for discharge from the hospital after a median time of 20–21 h after the end of anaesthesia and the median time to actual discharge ranged between 29.2 h and 43.2 h.

The numbers of patients reporting at least one adverse event throughout the study period were 150 (53%), 141 (49%) and 137 (48%) for the remifentanil+isoflurane, +enflurane and +propofol groups, respectively. As might be expected for patients receiving anaesthesia and an opioid, the most commonly reported adverse events were nausea, vomiting, shivering, muscle rigidity, hypotension and bradycardia (Table 5). Muscle rigidity was the most common drug-related adverse event during induction with an incidence of 6–7% across all three treatment groups. Hypotension and bradycardia were the most common intraoperative adverse events, requiring treatment with vasopressor/anticholinergic drugs.

Table 4

Time to qualification and time to actual discharge from the recovery room to the ward.

	Remifentanil +isoflurane	Remifentanil +enflurane	Remifentanil +propofol
All patients:			
Time to qualification for discharge (h)			
Median (Range)	0.6 (0.1–19.3)	0.6 (0.1–5.3)	0.5 (0.1–18.5)
(N)	(282)	(284)	(282)
Time to actual discharge (h)			
Median (Range)	1.2 (0.2–21.1)	1.1 (0.3–22.3)	1.2 (0.3–20.6)
(N)	(283)	(285)	(282)
Daycase patients:			
Time to qualification for discharge (h)			
Median (Range)	0.6 (0.1–19.3)	0.6 (0.1–3.2)	0.5 (0.1–18.5)
(N)	(147)	(148)	(148)
Time to actual discharge (h)			
Median (Range)	1.25 (0.3–19.3)	1.2 (0.3–5.3)	1.3 (0.3–18.5)
(N)	(148)	(149)	(148)
Inpatients:			
Time to qualification for discharge (h)			
Median (Range)	0.6 (0.1–4.1)	0.6 (0.1–4.6)	0.6 (0.1–18.4)
(N)	(135)	(136)	(134)
Time to actual discharge (h)			
Median (Range)	1.1 (0.2–21.1)	1.1 (0.3–22.3)	1.1 (0.3–20.6)
(N)	(135)	(136)	(134)

Table 5

Incidence (%) of adverse events.

	Remifentanil +isoflurane (N=285)	Remifentanil +enflurane (N=285)	Remifentanil +propofol (N=284)
Number of patients with any drug-related adverse events* and most frequent drug-related adverse events			
Induction (any drug-related A/E):	25 (9%)	21 (7%)	26 (9%)
Muscle rigidity	20 (7%)	16 (6%)	19 (7%)
Maintenance (any drug-related A/E):	16 (6%)	21 (7%)	19 (7%)
Hypotension	9 (3%)	14 (5%)	9 (3%)
Bradycardia	7 (2%)	4 (1%)	10 (4%)
Post-operative (any drug-related A/E):	73 (26%)	83 (29%)	57 (20%)
Shivering	20 (7%)	21 (7%)	18 (6%)
Nausea	39 (14%)	44 (15%)	21 (7%)
Vomiting	18 (6%)	23 (8%)	8 (3%)

* In the investigator's opinion almost certainly, probably or possibility related to treatment drug or of unknown causality.

Hypotension was reported for 3% of patients in the propofol and isoflurane treatment groups and in 5% of patients in the enflurane group. Bradycardia was recorded as an adverse event in 1–4% of the patients across all three treatment groups. Postoperative shivering was reported for 6–7% of the patients across the treatment groups. Patients in the propofol group experienced significantly less nausea (7%) and vomiting (3%) than those in the isoflurane or the enflurane groups (nausea 14% and 15%; vomiting 6% and 8%, respectively) ($P<0.05$). The occurrence of postoperative pain was low and was reported as an adverse event in <1% of patients.

Serious adverse events occurred in eleven patients, of which the following five were considered to be related to remifentanil. *Isoflurane group:* one patient experienced a respiratory arrest 28 min after termination of remifentanil; another patient reported hypoventilation lasting for 5 min, which occurred 16 min after termination of remifentanil. *Enflurane group*: One patient experienced severe vomiting about 4 h post surgery; one patient experienced an epileptic seizure-like attack approximately 6 h after surgery, which the investigator attributed equally to remifentanil and enflurane. *Propofol group*: one patient experienced apnoea, loss of consciousness and muscle rigidity 25 min after the end of anaesthesia.

Discussion

This study provides further comparative data on the recovery, efficacy and safety of remifentanil-based balanced anaesthesia with inhaled agents and a TIVA technique deploying propofol. Furthermore, this is the first reported study utilising remifentanil and enflurane anaesthesia.

Despite expected variations in durations of surgery, the study failed to demonstrate any differences in the extubation times or the overall recovery times following anaesthesia comprising remifentanil with either isoflurane, enflurane or propofol. Recovery is influenced not only by the anaesthetic dose but also by the longest-acting anaesthetic component. The starting doses of isoflurane or enflurane at 0.5 MAC and propofol at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ used in this study were lower than when these agents are used routinely with other opioids. However, as the protocol permitted optimal titration of the agents, all three regimens provided very good anaesthesia and stable haemodynamics. Furthermore, the responses to surgical stresses across all treatment groups were found to be lower than in earlier remifentanil studies which had deployed much higher starting concentrations of the hypnotic agent (e.g. 0.8% end-tidal isoflurane) (17–19). All three regimens provided intraoperative stability that is associated normally with opioid-based anaesthesia. However, in contrast to the delays in recovery that may be normally expected with opioid-based conventional anaesthesia, the unique elimination characteristic of remifentanil provided rapid and consistent emergence.

Overall, the numbers of patients experiencing reponses to surgical stresses in this study were much lower (19–28%) than reported (53–57%) for earlier, comparative, double-blind trials with remifentanil (17–19). This suggests that the anaesthetists in the

present, open design study were more easily able to titrate remifentanil to desired, optimum effects compared to the apparent complexity of similar clinical manoeuvres in earlier double-blind investigations.

Intubation of the trachea and skin incision represent some of the most stressful events and provide a significant test of potency of the analgesic agent. In this study, significantly fewer patients receiving remifentanil with isoflurane or enflurane responded to endotracheal intubation or to skin incision compared with patients treated with remifentanil and propofol. Overall, however, the response rates in all three groups were much lower than those reported in earlier studies of remifentanil with isoflurane/N_2O or with propofol (20, 21) and substantially lower than those reported for the widely established opioids such as fentanyl or alfentanil (17–19). The low intraoperative responses and the absence of hypotension or bradycardia during surgery tended to support the choice of the pre- and post-intubation infusion doses of remifentanil and its titratability with inhaled or intravenous hypnotic agents to provide optimum haemodynamics during anaesthesia.

The median times for the recovery parameters were short and highly consistent across all treatment groups, demonstrating the rapid offset of effect of remifentanil. Furthermore, orientation (i.e. Aldrete scores of $\geq$9) was rapid and occurred within a few minutes of extubation, demonstrating that profound intraoperative analgesia with remifentanil can be administered until the last surgical suture without consequential delays in recovery.

Patients in all three treatment groups qualified for recovery room discharge within 0.5–0.6 h after the end of anaesthesia irrespective of whether they had been admitted as a daycase or an inpatient. However, the overall median time of about 1.2 h for actual discharge from recovery room to the ward probably represented the time taken for the anaesthesia team personnel to be available to judge clinical suitability for discharge and the patient's actual discharge by the available nursing staff thereafter. The daycase patients qualified for discharge from the hospital within a median time of just under 3 h but their actual time of discharge approximated 4 h. The differences noted above between eligibility for and the actual discharge times, especially for the daycase patients, suggests that there was a potential for up to 50% reduction in hospital stay. However, in contrast, and probably because of hospital practice or administrative routine, patients admitted as inpatients were judged to qualify for discharge from the hospital at median times of 20–21 h despite having left the recovery room within an hour or so after end of anaesthesia. Although this study was not intended to specifically compare discharge times between the daycases and inpatients, the data are sufficiently compelling to recommend more formal investigations to establish whether the recent availability of short-acting agents such as propofol, sevoflurane or remifentanil will assist more institutions to consider performing certain surgical procedures on a daycase basis.

Most of the adverse events were typical of those associated with a potent μ-receptor opioid agonist and general anaesthesia. Postoperative pain was reported as an adverse event by less than 1% of the patients. Of the adverse events considered causally related to remifentanil, muscle rigidity at induction occurred in 6–7% of patients, indicating the rapid onset of remifentanil particularly if given as a rapid bolus. However, the muscle rigidity was mild or moderate and resolved rapidly. Intraoperative hypotension and bradycardia were seen in $\leq$5% of cases and were readily treatable with i.v. fluids or routinely used vasopressor and anticholinergic drugs, respectively.

Nausea and vomiting were more prevalent in the isoflurane and enflurane treatment groups than for patients treated with remifentanil and propofol, despite identical proportions of patients in each group having received antiemetic prophylaxis. This finding supports a recent report indicating that propofol may possess some antiemetic/antinausea properties (22). Hence, the combination of remifentanil and propofol may be of advantage to patients where there is a need to minimise this risk. Shivering was reported more frequently at centres with specific interest in this symptom during postoperative recovery.

In conclusion, anaesthesia employing combinations of remifentanil with either isoflurane, enflurane or propofol provided highly effective intraoperative analgesia and stable haemodynamics with rapid and almost identical emergence characteristics. The consistent recovery in turn produced identical times for recovery room stay for inpatients and daycases undergoing similar surgery. This suggests that institutions currently admitting inpatients may be able to accommodate certain short procedures, e.g. gynaecological laparoscopy or arthroscopic surgery, on a daycase basis.

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