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SCIENTIFIC ARTICLE

Sufentanil during anesthetic induction of remifentanil-based total intravenous anesthesia: a randomized controlled trial

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KEYWORDS
Acute pain;
Pain;
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Abstract
Background: Postoperative pain represents an important concern when remifentanil is used for total intravenous anesthesia because of its ultrashort half-life. Longer acting opioids, such as sufentanil, have been used during induction of remifentanil-based total intravenous anesthesia as a means to overcome this shortcoming. However, the effectiveness and safety of such strategy still lacks evidence from randomized clinical trials. Hence, we aimed to assess the postoperative analgesic efficacy and safety of a single dose of sufentanil administered during the induction of remifentanil-based total intravenous anesthesia.
Methods: Forty patients, scheduled for elective open abdominal surgery, were randomized to receive remifentanil-based total intravenous anesthesia with or without a single dose of sufentanil upon induction. We assessed the postoperative morphine consumption administered through a patient-controlled analgesia pump. Self-reported pain scores and the occurrence of nausea, vomiting, pruritus, agitation, somnolence and respiratory depression were also assessed up to 2 days after surgery.
Results: The mean difference between the sufentanil and control groups regarding morphine consumption in the post-anesthetic care unit and at 12, 24 and 48 h after surgery were −7.2 mg (95%CI: −12.5 to −2.1, $p < 0.001$), −3.9 mg (95%CI: −11.9 to 4.7, $p = 0.26$), −0.6 mg (95%CI: (−12.7 to 12.7, $p = 0.80$), and −1.8 mg (95%CI: (−11.6 to 15.6, $p = 0.94$), respectively. Neither self-reported pain nor the incidence of adverse events were significantly different between groups at any time point.

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Conclusion: Our findings suggest that the administration of sufentanil during induction of remifentanil-based total intravenous anesthesia is associated with decreased early postoperative opioid consumption.

PALAVRAS-CHAVE
Dor aguda;
Dor;
Opioide;
Anestesia intravenosa total

Sufentanil durante a indução da anestesia intravenosa total à base de remifentanil: ensaio clínico randômico

Resumo
Justificativa: A dor pós-operatória é uma grande preocupação quando o remifentanil é usado para anestesia intravenosa total devido à sua meia-vida ultracurta. Os opioides de ação mais longa, como o sufentanil, têm sido usados durante a indução de anestesia intravenosa total à base de remifentanil como um meio de superar essa deficiência. Porém, a eficácia e segurança de tal estratégia ainda precisam de evidências advindas de ensaios clínicos randômicos. Portanto, objetivamos avaliar a eficácia analgésica e a segurança pós-operatória de uma dose única de sufentanil administrada durante a indução de anestesia intravenosa total à base de remifentanil.
Métodos: Quarenta pacientes eletivamente agendados para cirurgia abdominal aberta foram randomizados para receber anestesia intravenosa total à base de remifentanil, com ou sem uma dose única de sufentanil, após a indução da anestesia. Avaliamos o consumo de morfina no pós-operatório, administrado através de uma bomba de analgesia controlada pelo paciente. Os escores de dor autorrelatados e a ocorrência de náusea, vômito, prurido, agitação, sonolência e depressão respiratória também foram avaliados até dois dias após a cirurgia.
Resultados: A diferença média entre os grupos sufentanil e controle em relação ao consumo de morfina em sala de recuperação pós-anestesia e após 12, 24 e 48 horas da cirurgia foi de -7,2 mg (IC 95%: -12,5 a -2,1, $p < 0,001$), -3,9 mg (IC 95%: -11,9 a 4,7, $p = 0,26$), -0,6 mg (IC 95%: (-12,7 a 12,7, $p = 0,80$) e -1,8 mg (IC 95%: -11,6 para 15,6, $p = 0,94$), respectivamente. Não houve diferença significativa tanto nos escores de dor autorrelatados, quanto na incidência de eventos adversos entre os grupos.
Conclusão: Nossos achados sugerem que a administração de sufentanil durante a indução de anestesia intravenosa total à base de remifentanil está associada à redução do consumo de opioides no pós-operatório imediato.

Introduction

Remifentanil has a unique pharmacokinetic/dynamic profile characterized by fast onset of action (1–2 min) with rapid equilibrium between the plasma and the biophase,[1,2] and by extensive metabolism by esterases resulting in an ultrashort half-life (3–10 min) and rapid recovery even after prolonged infusion. Hence, its most important clinical advantage is fast awakening without significant residual effects soon after infusion cessation.[2] However, due to its rapid metabolism, patients undergoing remifentanil-based total intravenous anesthesia (TIVA) may experience severe postoperative pain and usually require other potent analgesics either during and/or after surgery.[3,4]

A strategy to overcome the lack of residual analgesia of remifentanil involves the administration of longer acting opioids, such as sufentanil, during induction (and sometimes maintenance) of remifentanil-based TIVA. However, no previous randomized controlled trials have examined the efficacy and safety of such strategy. Additionally, there is reason to view that strategy with skepticism because, despite its long terminal elimination half-life (from 2.4 to 12.8 h),[5] sufentanil has a short context-sensitive half-time of about 20 min for 1 h infusions.[6–8] Hence, the present study aimed to assess the postoperative analgesic efficacy and safety of sufentanil administered as a single dose during the induction of remifentanil-based TIVA.

Methods

This was a phase IV randomized double-blind controlled clinical trial. The study was approved by the local ethics committee and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at ClinicalTrials.gov (http://clinicaltrials.gov) (NCT01777100, principal

investigator: Fernanda B. Fukushima, date of registration: January 28, 2013) Patient recruitment happened between April 26, 2013 and February 20, 2015 and patients were followed-up for 2 days after surgery. This manuscript adheres to the CONSORT statement.[9] The trial ended after the pre-planned number of patients concluded the intended follow-up.

Inclusion criteria

Adult patients (aged 18 years and older) with American Society of Anesthesiology (ASA) physical status 1–3, undergoing elective open abdominal surgery with planned TIVA.

Exclusion criteria

Another planned anesthetic technique besides TIVA.

Allergy to tramadol, metamizole, propofol, rocuronium, dexamethasone, sufentanil, remifentanil or morphine.

Self-reported use of the following group of drugs that promote extensive induction of cytochrome P450 within 7 days prior to surgery: carbamazepine, phenobarbital, rifampin, tobacco, phenytoin or *Hypericum perforatum*.

Self-reported alcohol consumption of more than 2 standard drinks per day for women and of more than 4 standard drinks per day for men.

Self-reported use of illicit drugs within 30 days prior to surgery.

Study protocol

Patients were invited to participate in the study on the day prior to surgery and were instructed regarding the use of the Patient-Controlled Analgesia (PCA) pump. We used a computer-generated simple random sequence to assign patients to one of two treatment arms. Allocation concealment was achieved by means of sealed, opaque and continuously numbered envelopes, which were matched with patients according to their order of inclusion in the study. The study coordinator (FBF) was responsible for the generation of the random sequence and for its concealment in opaque, numbered envelopes. A research assistant was responsible for the enrollment of participants on the day before surgery. Upon arrival at the operating theater, a research assistant would allocate each patient to the next sealed envelope containing the information on the group to which the patient had been randomized.

Patients were randomized to one of two groups:

Sufentanil Group: Patients received anesthesia induction with a single IV dose of sufentanil 0.5 $\mu g.kg^{-1}$. Five minutes after the administration of sufentanil, a propofol target-controlled infusion aiming at a Bispectral Index (BIS) between 40 and 50 was initiated. A remifentanil infusion of 0.1–0.3 $\mu g.kg^{-1}.min^{-1}$ was immediately started once a 10% elevation from baseline in mean arterial pressure or heart rate was observed with BIS of 40–50.

Control Group: Patients received anesthesia induction with a continuous remifentanil infusion of 0.5 $\mu g.kg^{-1}.min^{-1}$ for 5 min followed by a maintenance dose of 0.1–0.3 $\mu g.kg^{-1}.min^{-1}$ and propofol target controlled infusion aiming at BIS of 40–50.

All patients received ringer lactate infusion and 10 mg of dexamethasone in the operating room upon anesthesia induction. Once a BIS of $\leq$50 was reached, patients of both groups received rocuronium 0.6 $mg.kg^{-1}$ to facilitate tracheal intubation. Patients were ventilated with a N_2O/O_2 mixture and FiO_2 of 0.4. Patients were monitored continuously with ECG, non-invasive arterial pressure, BIS and pulse oximetry. For both groups the rate of remifentanil infusion was adjusted according to changes in mean arterial pressure and heart rate. When a 10% rise in mean arterial pressure or heart rate was observed, the infusion of remifentanil was increased by 0.1 $\mu g.kg^{-1}.min^{-1}$. Conversely, when a 10% reduction in mean arterial pressure or heart rate was noted, the infusion of remifentanil was decreased by 0.1 $\mu g.kg^{-1}.min^{-1}$.

Patients from both groups had their remifentanil infusion discontinued upon completion of the surgical procedure. All patients received IV analgesia with metamizole 1 g and tramadol 100 mg approximately 30 min before the completion of the procedure. Neuromuscular blockade was reversed with sugammadex to achieve train-of-four >0.9, and tracheal extubation was performed upon eye opening and the presence of spontaneous ventilation.

All patients received IV metamizole 1 g every 6 h and tramadol 100 mg every 6 h, as well as morphine-PCA (1 mg bolus dose with lockout interval of 10 min). Upon emergence from anesthesia all patients reporting severe pain (verbal rating scale 8–10) and/or displaying signs of intense pain (e.g., agitation, facial grimacing, moaning) were given a morphine 3 mg bolus.

Baseline assessment

We compared patients at baseline concerning age, sex, body mass index, ASA physical status, type and duration of surgical procedure.

Outcomes

We recorded patient's mean arterial pressure and heart rate at the following time points: baseline, upon induction of anesthesia, after tracheal intubation, at the beginning of the operation and subsequently at 5, 10, 15, 20, 25, 30, 45 and 60 min after the initial surgical incision, upon completion of surgery and immediately after tracheal extubation. We also documented the duration of anesthesia and the time interval between completion of the surgical procedure and awakening (spontaneous eye opening) in minutes.

We also assessed patients at 15, 30, 60 min in the Post-Anesthesia Care Unit (PACU), at discharge from that unit, and on the morning of postoperative days 1 and 2 for the following outcomes:

Morphine consumption

Pain verbal rating scale (from 0 to 10, where 0 means no pain and 10 means the worst imaginable pain).

Occurrence of nausea, vomiting, pruritus, sedation, agitation and respiratory depression.

Respiratory depression was defined as fewer than 10 respiratory movements per minute. We used the Ramsay Sedation Scale to assess sedation and agitation.[10] The prespecified primary outcome was morphine consumption 24 h after surgery.

When patients received a 3 mg bolus of morphine upon emergence from anesthesia, that dose was counted under the total morphine consumption from 0 to 15 min in PACU.

Blinding

Patients, outcome assessors and the researcher responsible for statistical analyses were blinded to the allocation of patients to the different treatment groups.

Statistical analyses

We presented summary descriptive statistics as total numbers and percentages for proportions, mean and standard deviations for continuous data. We used standardized differences to assess imbalances between baseline characteristics of the two groups. We examined visually the histograms of ordinal and continuous variables to check if data distribution was normal. Because none of those distributions were normal, we used nonparametric bootstrap based on the Bias-Corrected and accelerated method to calculate confidence intervals and *p*-values for mean differences between treatment groups regarding postoperative morphine consumption and pain scores by drawing 10,000 replicates from the data.[11,12] We calculated risk ratios with 95% Confidence Intervals for comparisons concerning the incidence of opioid-related adverse events.[13] All analyses were performed on an intention-to-treat basis. We adopted a value of 0.05 for statistical significance. We used the R software version 3.3.2[14] for statistical analyses. Within the R software, we used the package ''wBoot'' version 1.0.3 (https://CRAN.R-project.org/package=wBoot) for the bootstrap analyses described above.

Sample size

We calculated a total sample size of 40 individuals based on an estimated difference of morphine consumption of 10 mg within 24 h after surgery, a standard deviation of 9 mg, and an alpha value of 0.05 for statistical significance in a two-sided *t*-test with 80% power.[15]

Protocol deviations

All patients complaining or presenting signs of severe pain upon emergence from anesthesia received a 3 mg IV dose of morphine. That dose was not part of our original protocol and was implemented because when we pilot tested the protocol some patients reported intense pain that was not adequately relieved by the planned 1 mg PCA bolus. Patients from the pilot test were not included in the final analyses.

Results

There were 21 patients in the Sufentanil Group and 19 in the Control Group. Fig. 1 shows the flow diagram of participants through each stage of the study. At baseline there were no clinically significant differences between groups regarding patients' age, sex, body mass index, ASA physical status, type and duration of surgical procedures (Table 1).

Duration of anesthesia was similar between the Sufentanil Group (206 min, SD = 58 min) and the Control Group (195 min, SD = 52 min) with a mean difference of 11 min (95% CI −21.8 to 45.8, $p = 0.53$). Emergence time and total time in PACU were also similar between groups with mean differences of 0.2 min (95% CI −4.1 to 4.4, $p = 0.70$) and −5.4 min (95% CI −25.7 to 12.9, $p = 0.50$), respectively. In addition, the number of hours between the end of surgery and the evaluation by the outcome assessor on postoperative days 1 and 2 was also similar between groups with a mean difference of 1.4 hour (95% CI −0.8 to 6.3, $p = 0.74$) and 1.6 hour (95% CI −0.6 to 6.6, $p = 0.68$), respectively. During the intra-operative period there were neither clinical nor statistical differences between groups regarding mean arterial pressure and heart rate (Fig. 2).

Whereas 11 (58%) of 19 patients in the Control Group had severe pain upon arrival in PACU requiring a 3 mg morphine bolus, only 3 (14%) of 21 patients in Sufentanil Group had a similar experience (RR = 0.25, 95% CI 0.08–0.75, $p = 0.007$). Table 2 shows the postoperative morphine consumption at different time points, and Table 3 describes the postoperative pain assessments. Table 4 shows the frequency of nausea, vomiting, pruritus, sedation, agitation and respiratory depression after surgery. All records of sedation in PACU were mild, corresponding to Ramsay 3 level (i.e., patients were responsive to commands only).

Discussion

The main finding of the present study is that a single low dose of sufentanil during induction of remifentanil-based TIVA significantly decreases morphine consumption (mean 7.2 mg) during the immediate postoperative period, but not at 12, 24 and 48 h after surgery when compared with remifentanil-based TIVA alone. This effect reflects better analgesia and was more pronounced during the first 15 min upon admission to PACU. This finding may seem counterintuitive considering the short context-sensitive half-time of sufentanil of about 20 min for 1 h infusions.[5] Indeed, a previous pharmacokinetic study that assessed plasma concentrations of sufentanil in surgical patients following a single 5 $\mu g.kg^{-1}$ bolus found that its concentration dropped by 98% within 30 min after administration.[6] However, our results are consistent with the long terminal elimination half-life of sufentanil, which ranges from 2.7 to 12.8 h,[6–8] and with the finding that the minimum effective sufentanil serum concentration for analgesia varies greatly among patients but is usually above 0.03 $ng.mL^{-1}$,[16] a level that must have been present for most of our patients in the sufentanil group in the immediate postoperative period according to the pharmacokinetic data reported by Bovill et al.[6] It is, therefore, plausible, that patients undergoing shorter (or less painful) procedures might also benefit from a single dose of sufentanil. Importantly,

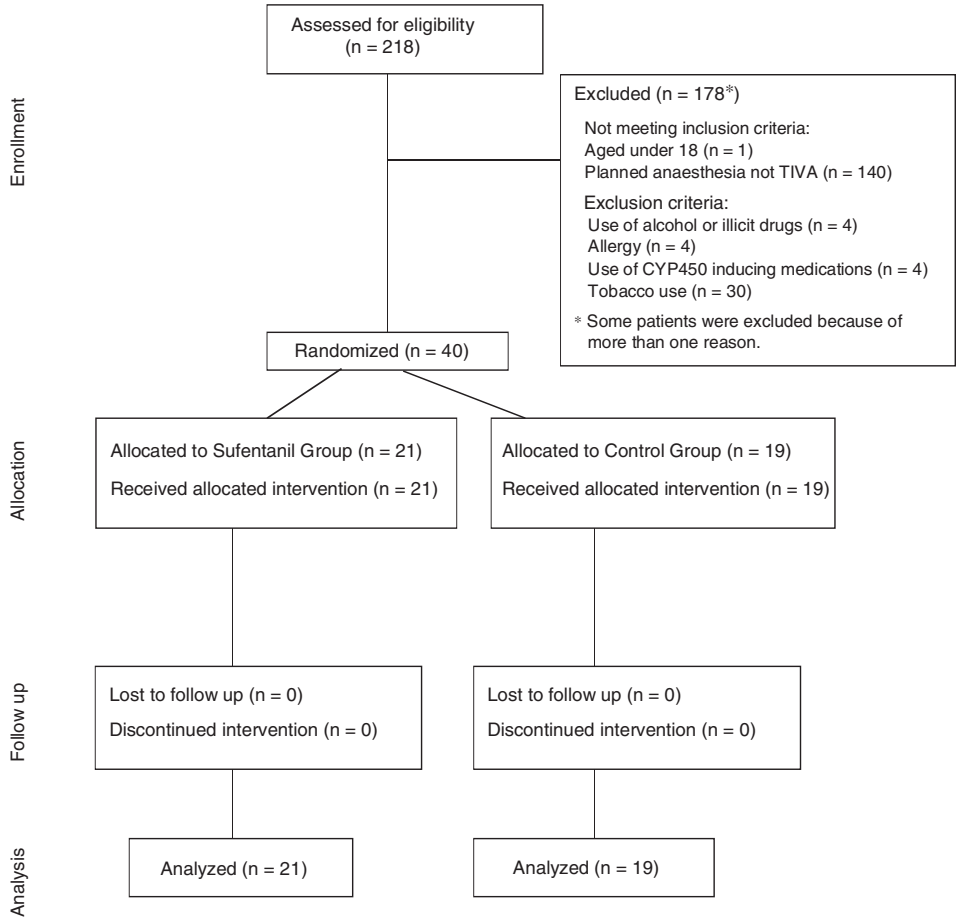

Figure 1 Diagram showing the flow of participants through each stage of the trial.

Table 1 Patient baseline characteristics and features of surgical procedures performed according to treatment group.

Baseline characteristics	Sufentanil Group	Control Group	Standardized difference
Age (years)[a]	52.2 (10.1)	52.0 (16.4)	0.04
Female[b]	16 (76.2%)	16 (84.2%)	0.20
Body mass index[a]	28.1 (5.3)	26.8 (2.5)	0.05
ASA[b]			0.72
ASA 1	10 (47.6%)	15 (78.9%)	
ASA 2	10 (47.6%)	4 (21.1%)	
ASA 3	1 (4.8%)	0	
Surgical procedure[b]			0.67
Cholecystectomy	4 (19.0%)	7 (36.8%)	
Hysterectomy	13 (61.9%)	11 (57.9%)	
Gastrectomy	1 (4.8%)	1 (5.3%)	
Splenectomy	1 (4.8%)	0 (0%)	
Exploratory laparotomy	2 (9.5%)	0 (0%)	
Duration of surgery[a] (min)	157.4 (53.1)	140.5 (41.1)	0.07

[a] Data presented as mean (standard deviation).
[b] Data presented as absolute number (%).
ASA, American Society of Anesthesiology physical status classification.

the better analgesic profile in PACU was not associated with higher incidence of adverse effects or delayed awakening. To the best of our knowledge, this is the only study examining the use of sufentanil or other opioids during anesthesia induction of remifentanil-based TIVA.

A pilot run of our protocol led us to allow the administration of a 3 mg bolus of morphine upon awakening as

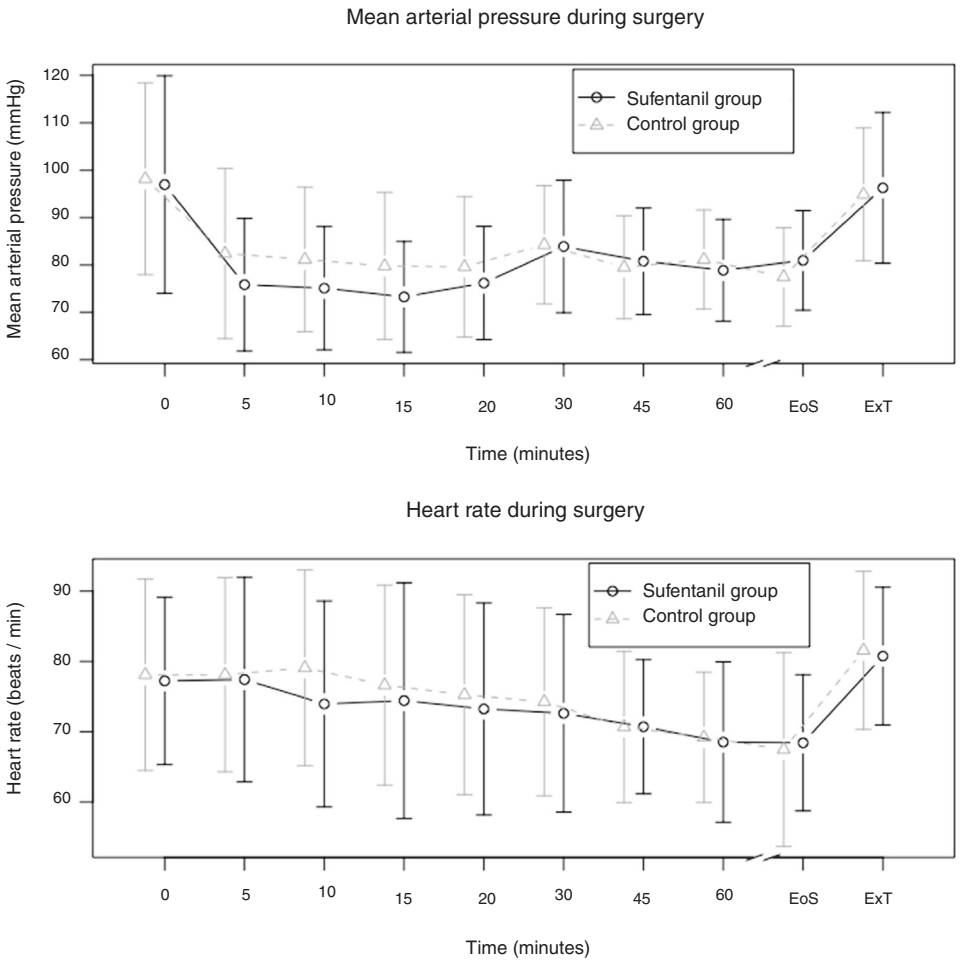

Figure 2 Mean arterial pressure and heart rate variation during anesthesia.

Table 2 Morphine consumption after surgery.

Morphine consumption	Sufentanil Group Mean (SD)	Control Group Mean (SD)	Mean difference (95% CI)[a]	*p*[a]
In PACU				
0–15 min	2.1 (2.0)	5.3 (3.1)	−3.2 (−4.9 to −1.8)	<0.001
16–30 min	1.9 (1.7)	2.8 (2.7)	−0.9 (−2.4 to 0.3)	0.20
31–60 min	2.3 (2.5)	3.8 (3.3)	−1.5 (−3.3 to 0.23)	0.12
61 min to discharge from PACU	2.5 (3.1)	4.1 (4.0)	−1.6 (−3.8 to 0.5)	0.17
Total in PACU	8.8 (7.0)	16.0 (10.1)	−7.2 (−12.5 to −2.1)	<0.001
12 h after surgery	20.6 (13.4)	24.5 (12.7)	−3.9 (−11.9 to 4.7)	0.26
24 h after surgery	32.3 (21.9)	32.9 (19.3)	−0.6 (−12.7 to 12.7)	0.80
48 h after surgery	41.1 (20.9)	39.3 (20.9)	1.8 (−11.6 to 15.6)	0.94

PACU, Post-Anesthesia Care Unit.
[a] *p*-Values and 95% CI were calculated using nonparametric bootstrap based on the Bias-Corrected and accelerated method.

some patients reported intense pain despite pre-emptive analgesia with tramadol and metamizole. Unfortunately, it was not feasible to compare pain scores upon awakening because of residual sedation. However, the fact that the proportion of patients requiring the 3 mg bolus of morphine upon awakening was 4 times lower in the sufentanil group is consistent with improved immediate postoperative analgesia provided by a single dose of sufentanil upon induction of remifentanil-based TIVA.

Despite the lower morphine consumption by patients in the sufentanil group during their first minutes in the PACU, the pain scores did not differ between groups when assessed 15 min after admission to PACU and onwards. Several reasons may explain this divergence. Firstly, self-reports of pain

Table 3 Pain after surgery as measured by 0–10 pain verbal rating scale.

Postoperative pain	Sufentanil Group Mean (SD)	Control Group Mean (SD)	Mean difference (95% CI)[a]	p[a]
At PACU				
15 min	5.6 (3.4)	6.6 (4.2)	−1.0 (−3.2 to 1.4)	0.10
30 min	5.2 (3.3)	5.8 (4.1)	−0.6 (−2.9 to 1.7)	0.17
60 min	4.2 (3.5)	5.3 (3.9)	−1.1 (−3.3 to 1.2)	0.07
At discharge from PACU	1.8 (2.6)	2.4 (3.0)	−0.6 (−2.4 to 1.1)	0.06
Postoperative day 1	1.6 (2.0)	1.2 (2.2)	0.6 (−1.0 to 1.6)	0.35
Postoperative day 2	1.2 (1.9)	1.2 (1.8)	0.0 (−1.0 to 1.2)	0.10

PACU, Post-Anesthesia Care Unit.
[a] p-Values and 95% CI were calculated using nonparametric bootstrap based on the Bias-Corrected and accelerated method.

Table 4 Frequency of nausea, vomiting, pruritus, sedation, agitation and respiratory depression after surgery.

Adverse events	Sufentanil Group	Control Group	Risk ratio (95% CI)	p
In PACU				
Nausea	3 (14.3%)	6 (31.6%)	0.45 (0.13–1.56)	0.21
Vomiting	0 (0%)	1 (5.2%)	0.30 (0.01–7.02)	0.46
Pruritus	0 (0%)	1 (5.2%)	0.30 (0.01–7.02)	0.46
Sedation	10 (47.6%)	4 (21.1%)	2.26 (0.85–6.02)	0.10
Agitation	7 (33.3%)	8 (42.1%)	0.79 (0.35–1.77)	0.48
Respiratory depression	1 (4.8%)	1 (5.2%)	0.91 (0.06–13.50)	1
Between discharge from PACU and assessment on postoperative day 2				
Nausea	0 (0%)	3 (15.9%)	0.13 (0–0.36)	0.17
Vomiting	2 (9.5%)	1 (5.2%)	1.81 (0.18–18.39)	0.94
Pruritus	1 (4.8%)	2 (10.5%)	0.45 (0.05–4.60)	0.60
Sedation	0 (0%)	0 (0%)	0.91 (0.02–43.71)	1.00
Agitation	0 (0%)	0 (0%)	0.91 (0.02–43.71)	1.00
Respiratory depression	0 (0%)	0 (0%)	0.91 (0.02–43.71)	1.00

PACU, Post-Anesthesia Care Unit.

intensity were restricted to patients' sensations at specific time-points (e.g., at 15 and 30 min) and not to time intervals (e.g., from 0 to 15 min); and may therefore reflect the cumulative analgesic effect of morphine doses administered through PCA before each assessment. Secondly, differences in opioid consumption and self-reported pain scores have been described and attributed to a myriad of factors ranging from inter-individual variability in opioid sensitivity and perception of pain to patients' training in use of PCA.[17,18] Thirdly, our study was underpowered to detect differences in morphine consumption beyond the first 15 min.

This study has several limitations. Firstly, any effect of sufentanil on postoperative analgesia should be most significant within the first several minutes/hours after surgery (based on pharmacokinetics); yet, we adopted morphine consumption at 24 h postoperative as our primary outcome. Secondly, although the remifentanil doses adopted in the present study could induce opioid tolerance and hyperalgesia,[19] we did not include such entities as outcomes. Thirdly, our sample size was small and somewhat heterogeneous, involving mostly middle-aged adults, ASA 1–2, undergoing various open abdominal surgeries with a mean duration of 150 min. Hence, our results may not be generalizable to other groups of patients. Fourthly, our sample size may have provided insufficient power to assess each secondary outcome. Fifthly, our anesthetic protocol included N_2O which is not a standard practice for TIVA. However it is unlikely that the use of N_2O compromised our results since it was part of the anesthetic protocol for both groups. Finally, we did not perform adjustment for multiple comparisons considering all secondary outcomes. However, there are some strong arguments against routine use of p-values and confidence intervals adjusted for multiple comparisons in clinical trials. As argued by Rothman,[20] adjustment for multiple comparisons reduce the probability of Type I errors at the expense of increasing the probability of Type II errors, which should be considered illogical without some consideration about the estimated frequency of each type of error. Nevertheless, even considering common misconceptions regarding tests of statistical significance and adjustments for multiple comparisons,[21] the lower morphine consumption in PACU by the Sufentanil Group would remain significant even after correcting for 50 multiple comparisons using the conservative Bonferroni method.[22]

Future studies assessing sufentanil or other anesthetic strategies at induction of remifentanil-based TIVA should define their primary analgesic outcome within the first several minutes after emergence, enroll larger samples of patients to increase statistical power for the assessment of secondary outcomes, perform cost-effectiveness analyses and evaluate the occurrence of acute opioid tolerance and hyperalgesia.

Conclusion

Our study provides evidence that the use of a low dose of sufentanil during anesthetic induction of remifentanil-based TIVA is associated with reduced discomfort on emergence, decreased opioid consumption in the immediate postoperative period but not at 12, 24 and 48 h after surgery when compared with remifentanil-based TIVA alone.

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Conflicts of interest

The authors declare no conflicts of interest.

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