

ORIGINAL ARTICLE

The impact of intra-operative sufentanil dosing on post-operative pain, hyperalgesia and morphine consumption after cardiac surgery

J. Fechner, H. Ihmsen, J. Schüttler, C. Jeleazcov

Department of Anaesthesiology, University of Erlangen-Nürnberg, Erlangen, Germany

Correspondence

Jörg Fechner

E-mail:

joerg.fechner@kfa.imed.uni-erlangen.de

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Conflicts of interest

None of the authors has any conflict of interest.

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Abstract

Background: There is an ongoing debate whether opioids when used for intra-operative analgesia may enhance post-operative pain. We studied the effect of two different intra-operative dosings of sufentanil on post-operative morphine consumption, pain and hyperalgesia after cardiac anaesthesia.

Methods: Forty-two male patients (age: 48–74 years) undergoing first-time coronary artery bypass graft surgery were randomized to one of two groups receiving total intravenous anaesthesia with propofol and a target controlled infusion of sufentanil with a target of 0.4 ng/mL (group SL, $n = 20$) or 0.8 ng/mL (group SH, $n = 22$) plasma concentration. Post-operative morphine requirement in the first 48 h was assessed using patient-controlled analgesia (PCA). Pain rating during deep inspiration, and the extent of primary and secondary hyperalgesia near the sternotomy wound were assessed.

Results: The post-operative morphine requirements in the first 48 h were 0.68 ± 0.21 mg/kg in group SL and 0.96 ± 0.44 mg/kg in group SH ($p < 0.05$). In group SL, pain during deep inspiration was significantly lower on the first post-operative day ($p < 0.05$). Primary hyperalgesia had its maximum on the second and third post-operative day, without a difference between the two groups. The extent of secondary mechanical pinprick hyperalgesia was not different between the groups.

Discussion: Intra-operative dosing of sufentanil significantly influenced post-operative morphine consumption, pain and hyperalgesia. For cardiac anaesthesia in combination with propofol, a sufentanil target concentration of 0.4 ng/mL may be preferable.

1. Introduction

Post-operative pain and analgesic treatment still remains a challenge in daily perioperative medicine (Carr and Goudas, 1999; Wu and Raja, 2011). An investigation in 1490 surgical inpatients revealed moderate-to-severe pain in 41% of the patients on the day of surgery, decreasing to 15% on the fourth post-operative day (Sommer et al., 2008). Preoperative pain, anxiety, age, type of surgery and psychological distress were found to be significant predictors of the

development of post-operative pain and analgesic consumption (Ip et al., 2009). In addition, Guignard et al. reported a higher post-operative morphine consumption after higher intra-operative dosing of remifentanil (Guignard et al., 2000).

Over the last decade, there has been increased interest in opioid-induced hyperalgesia (Angst and Clark, 2006). Numerous studies demonstrated opioid-induced hyperalgesia in animals (Mao et al., 2002; Celerier et al., 2006; Cabanero et al., 2009) and in volunteers using experimental pain models (Compton

What's already known about this topic?

- It has been shown that remifentanyl, when used for intra-operative analgesia, can cause opioid-induced hyperalgesia in form of enhanced post-operative pain and increased post-operative morphine consumption.

What does this study add?

- Intra-operative dosing of sufentanil significantly influenced post-operative morphine consumption, pain and hyperalgesia. For cardiac anaesthesia in combination with propofol, a sufentanil target concentration of 0.4 ng/mL may be preferable.

et al., 2003; Hood et al., 2003). However, the findings in patient studies were less clear, with confirmatory (Joly et al., 2005) as well as negative results (Cortinez et al., 2001). The underlying cellular mechanisms of opioid-induced hyperalgesia are also not yet clear, and some findings suggest that this phenomenon is not directly mediated by opioid receptors (Juni et al., 2007).

Whereas post-operative pain, analgesic consumption and opioid-induced hyperalgesia has been discussed extensively for remifentanyl (Angst et al., 2003; Lee et al., 2005; Lahtinen et al., 2008), there are only very few reports considering intra-operative administration of sufentanil, either as case report (Devulder, 1997) or in animal studies (Freye and Levy, 2010; Minville et al., 2010). Sufentanil is routinely used as intra-operative analgesic for cardiac surgery, and it seems to have the advantage of cardioprotection against hypoxia-reperfusion injury (Lemoine et al., 2011). The use of sufentanil as intra-operative analgesic also resulted in a better performance with regard to post-operative pain therapy (Lison et al., 2007).

Therefore, it was the aim of the present study to investigate the hypothesis that intra-operative dosing of sufentanil has a significant impact on post-operative morphine consumption, pain and hyperalgesia in patients undergoing coronary artery bypass graft (CABG) surgery.

2. Methods

This randomized, double-blinded, prospective study was performed in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all subjects. The study was approved by the Institutional

Ethics Committee (Ethikkommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany).

2.1 Subjects

After written informed consent, male adult patients undergoing elective first-time CABG surgery were enrolled in this study. Inclusion criteria were an age between 40 and 75 years, American Society of Anesthesiologists physical status of 3 or less and a left ventricular ejection fraction of at least 40%. Patients with diabetes mellitus or a medical history of renal, neurological or chronic inflammatory disease were excluded from the study. Further exclusion criteria were drug abuse as well as the use of non-steroidal anti-inflammatory drugs or opioids for pain therapy before the start of the study.

2.2 Anaesthesia

Following a pre-medication with 7.5 mg midazolam p.o. (Dormicum®, Roche Pharma, Grenzach-Wyhlen, Germany), anaesthesia was induced and maintained with continuous infusions of propofol (Disoprivan® 2%, AstraZeneca, Wedel, Germany) as anaesthetic and sufentanil (Sufenta®, Janssen-Cilag, Neuss, Germany) as analgesic drug. Intubation was facilitated with 0.15 mg/kg cisatracurium (Nimbex®, Glaxo-SmithKline, München, Germany). During induction, propofol was administered as target-controlled infusion (TCI) using the pharmacokinetic model of Marsh (Marsh et al., 1991), targeting plasma concentrations between 2.5 and 4 µg/mL. After skin incision, propofol was administered by a closed-loop control system (IvFeed 5.31, Department of Anaesthesiology, University Hospital Erlangen, Germany; Fechner et al., 2003) using the bispectral index (BIS™, Aspect Medical Systems, Newton, MA, USA, Rev. 3.31) as pharmacodynamic endpoint and targeting a BIS value between 35 and 45. Sufentanil was administered as TCI using the pharmacokinetic model of Gepts (Gepts et al., 1995). The patients were randomized into two treatment groups, which were different with respect to the target concentration: sufentanil low (SL) with 0.4 ng/mL, and sufentanil high (SH) with 0.8 ng/mL plasma target concentration. These target concentrations were kept constant from at least 20 min before skin incision until last skin suture. During induction of anaesthesia, the sufentanil target concentrations were 0.4 to 1.5 ng/mL. Sufentanil was stopped at last skin suture. After the end of the surgery, the patients were transferred to the intensive care unit (ICU) and the

propofol infusion was continued for further 2–3 h with an infusion rate of 2.5 mg/kg/h. The patients and all examiners involved in the assessment of the clinical endpoints were blinded with respect to the study group allocation.

2.3 Post-operative pain control

At admission in the ICU, the patient controlled analgesia (PCA) device (Graseby™ PCA 3300 PCA, Smiths Medical Deutschland, Kirchseeon, Germany) was connected, delivering bolus doses of 2 mg morphine (MSI Mundipharma®, Mundipharma, Limburg, Germany) with a lockout time of 10 min. As long as the patient was unconscious due to ongoing sedation with propofol, morphine dosing was nurse controlled using the PCA infusion device. As soon as the patient had regained consciousness, he was extubated and morphine dosing was controlled by himself using the PCA infusion device. Forty-eight hours after ICU admission, morphine PCA was stopped, and the analgesic regimen was continued with buprenorphine (Temgesic®, RB Pharmaceuticals, Berkshire, UK). Between admission at the ICU and extubation, piritramide i.v. (Dipidolor®, Janssen-Cilag, Neuss, Germany) was allowed as additional rescue analgesic. To determine the total opioid consumption, the doses of piritramide were converted into morphine equivalent doses, assuming that 15 mg piritramide are equivalent to 10 mg morphine (Freye, 1987). Non-steroidal anti-inflammatory drugs were excluded throughout the complete 48 h post-operative study period. Post-operative pain at rest and during deep inspiration was rated by the patient using a numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain imaginable). This pain rating was performed post-operatively in the evening on the day of the surgery (post OP 0) after the PCA had been started, and three times per day on the following two days (post OP 1 and post OP 2). The average of the three pain ratings was used for further analysis during the 48 h after ICU admission. On the following 5 days, after patients had been transferred to the ward, pain at rest and during deep inspiration was recorded once per day.

2.4 Sensory testing and assessment of hyperalgesia

Sensory testing was performed 2 cm lateral to the sternotomy wound with von Frey filaments (Stoelting, Chicago, IL, USA) of 8, 16, 32, 64, 128, 256, 362 and 512 mN. The pain was rated by the patient using a NRS from 0 (no pain) to 10 (worst pain imagin-

able). For stimulus-response analysis, the pain testing with all von Frey filaments was performed on the day before surgery (baseline) and once per day on the first seven post-operative days. Stimulus-response curves in each patient on the different days were obtained by fitting a sigmoid model to the data:

$$\text{NRS} = \text{NRS}_{\max} \cdot \frac{F^\gamma}{F^\gamma + F_{50}^\gamma} \quad \text{where } \text{NRS}_{\max} \text{ is the}$$

maximum pain rating, F is the force of the von Frey filament, F_{50} is the force that induces a half-maximum effect of NRS, and γ characterizes the steepness of the stimulus-response curve. Primary hyperalgesia, defined as sensitization of nociceptive nerve endings at the site of injury, was assessed at the first to seventh post-operative day as the area between the stimulus-response curve at baseline and the stimulus-response curve at the respective post-operative day (Sandkühler, 2009). The area was calculated such that a positive value means a left shift of the stimulus-response curve, and a negative value a right shift of the stimulus-response curve compared to baseline.

The extent of secondary mechanical pinprick hyperalgesia was determined with a 256 mN von Frey filament along three parallel lines orthogonal to the sternotomy wound at its upper, middle and lower part on the right side, starting at a distant point (10 cm from the wound) and moving gradually towards the wound, until the patient reported increased pain. The average of these three distances between the boundary of the hyperalgesic area and the sternotomy wound was taken as a measure of secondary hyperalgesia, representing changes in the processing of sensory information in the central nervous system (Sandkühler, 2009). This test was performed once every day on the first seven post-operative days.

2.5 Side effects

The cognitive function of the patients was assessed using the mini-mental state test (Folstein et al., 1975), a brief 30-point questionnaire, which rates the following skills: orientation to time and place, registration, attention and calculation, recall, language (speech, writing, following a command) and drawing. Any score greater than or equal to 25 (out of 30) points is effectively normal. Below this, scores can indicate severe (≤ 9 points), moderate (10–20 points) or mild (21–24 points) degree of cognitive dysfunction. The mini-mental state test was performed on the day before surgery (baseline) and once per day on the first seven post-operative days.

Patients were further monitored for typical opioid side effects like post-operative nausea and vomiting (PONV), sedation and constipation.

2.6 Statistics

Primary clinical endpoints of the study were (1) cumulative post-operative morphine consumption during 48 h after ICU admission; (2) pain rating under deep inspiration during 48 h after ICU admission; (3) primary hyperalgesia during first 7 days after surgery; and (4) extent of pinprick hyperalgesia near the sternotomy wound during first 7 days after surgery. The score of the mini-mental state test as well as the presence of constipation and post-operative nausea and vomiting (PONV) during first 7 days after surgery were analysed as secondary outcomes of the study.

Data were tested for normal distribution by the Shapiro–Wilks test. Patients' characteristics, anaesthesia data and the cumulative morphine consumption were analysed by the unpaired *t*-test or by the Mann–Whitney test, respectively. Time-related changes of the pain rating and the extent of primary and secondary hyperalgesia were analysed by repeated measurements analysis of variance (RM-ANOVA) with the sufentanil target as factor, or by Friedman's ANOVA, respectively. Comparisons between the two groups SH and SL at specific days were performed by the unpaired *t*-test or the Mann–Whitney test with Bonferroni correction, respectively. The extent of primary hyperalgesia was considered significant if the area between the stimulus-response curves at baseline and at the respective post-operative day was different from zero. This was tested with the one sample *t*-test or the Wilcoxon test with Bonferroni correction, respectively.

The scores of the mini-mental state test were analysed for time-related effects within the groups by Friedman's ANOVA, and by the Wilcoxon test with Bonferroni correction for the comparison with baseline. The groups were compared with the Mann–Whitney test with Bonferroni correction. The incidence of side effects was analysed by the χ^2 test or Fisher's exact test, respectively. The level of significance was $p < 0.05$ for all tests.

Regarding the morphine consumption as primary endpoint, a sample size estimation for the unpaired *t*-test revealed, that one needed at least 17 patients per group to detect a distinct standardized effect of 1 (i.e., the difference between the means is as large as the standard deviation) with a significance level of $p < 0.05$ and a power of 80%. Statistic analysis was performed with Statistica 6.0 (StatSoft Inc, Tulsa, OK, USA).

3. Results

Forty-two patients were enrolled in the study (20 in group SL, 22 in group SH), and received anaesthesia with propofol and sufentanil with the defined target concentrations. Three cases were lost during follow-up due to post-operative complications in the ICU ($n = 1$) or retraction of consent by the patient to further participate in the study ($n = 2$). Five cases had to be excluded from the analysis due to incomplete documentation of the morphine consumption ($n = 4$) or due to post-operative use of metamizole ($n = 1$). Thus, the data of 34 patients could be analysed: 18 in group SL, and 16 in group SH. The two groups did not differ in patient characteristics and anaesthesia data, except for the intra-operative consumption of sufentanil (Table 1).

Table 1 Patients' characteristics ($n = 34$) and anaesthesia data.

	Sufentanil target concentration		<i>p</i> -value
	0.4 ng/mL	0.8 ng/mL	
Sex (male/female)	18/0	16/0	–
Age (year)	62 ± 7	59 ± 6	0.28
Body weight (kg)	83 ± 12	82 ± 11	0.89
Height (cm)	176 ± 6	173 ± 6	0.12
BMI (kg/m ²)	26.7 ± 2.6	27.2 ± 3.4	0.60
Duration of anaesthesia (min)	235 ± 46	226 ± 46	0.63
Duration of CPB (min)	64 ± 19	65 ± 25	0.93
Time to extubation (h)	5.9 ± 2.8	4.5 ± 2.1	0.43
Propofol (mg/kg/h)	7.0 ± 1.2	6.7 ± 1.4	0.43
Sufentanil (µg/kg/h)	0.55 ± 0.04	1.03 ± 0.08	<0.0001
BIS	40.1 ± 4.7	41.5 ± 4.3	0.25

Data are expressed as mean ± SD. BMI, body mass index; CPB, cardio pulmonary bypass; BIS, mean value of the bispectral index between intubation and end of anaesthesia. *P*-value: significance level of the difference between the two groups.

Table 2 Cumulative post-operative opioid consumption in the first 48 h.

	Sufentanil target concentration		<i>p</i> -value
	0.4 ng/mL	0.8 ng/mL	
Opioids (mg/kg) until extubation	0.18 (0–0.36)	0.15 (0–0.42)	0.48
Morphine PCA (mg/kg) after extubation	0.68 ± 0.21	0.96 ± 0.44	0.03

Data are expressed as mean ± SD and median (range). PCA, patient-controlled analgesia. Opioid consumption until extubation includes nurse-controlled morphine and piritramide doses (expressed as morphine equivalent dose). *P*-value: significance level of the difference between the two groups.

3.1 Post-operative opioid consumption

With regard to the cumulative morphine PCA requirement after extubation during the first 48 h after ICU admission, there was a significant effect of the intra-operative analgesic regimen (Table 2). Patients in group SL required a smaller amount of morphine administered via PCA when compared to those of group SH. In contrast, the total doses of morphine and piritramide given between ICU admission and extubation were not different.

3.2 Pain rating

There were significant effects of time (*p* < 0.001) and sufentanil target (*p* < 0.005) on the post-operative pain during deep inspiration (Fig. 1). On the day of the

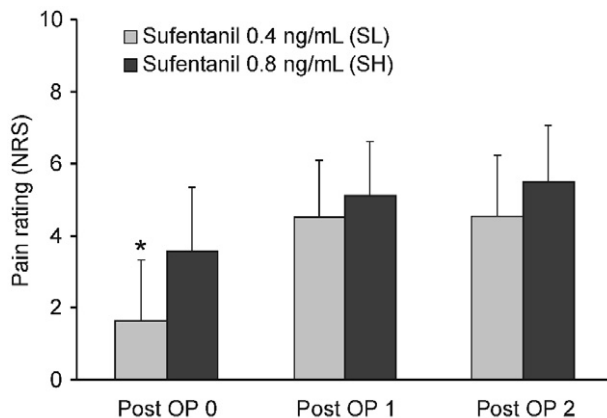


Figure 1 Pain rating during deep inspiration. Data are expressed as mean ± SD. Post OP 0, post-operatively on the day of the surgery; post OP 1, post-operatively on the day following the day of the surgery; post OP 2, post-operatively on the second day following the day of the surgery; SH, high sufentanil target group; SL, low sufentanil target group. **p* < 0.05 low sufentanil target group vs. high sufentanil target group on the day of surgery.

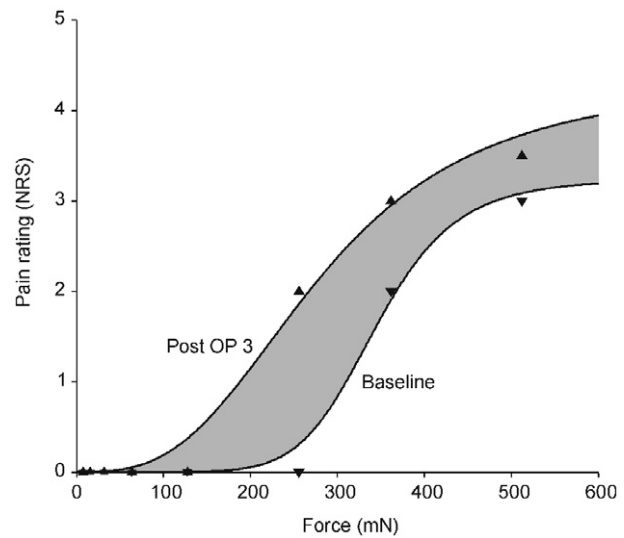


Figure 2 Shift of the stimulus-response curve in one typical patient with a sufentanil target of 0.4 ng/mL. Shown are the measured pain ratings at baseline (lower triangles) and at the third post-operative day (upper triangles), together with the fitted sigmoid stimulus-response curves. The shaded area between the two curves was taken as a measure of primary hyperalgesia, where a positive area value means a left shift of the stimulus-response curve, and a negative area value a right shift of the stimulus-response curve compared to baseline.

surgery (post OP 0), post-operative pain was significantly smaller in the group SL compared to the group SH (*p* = 0.017). This difference disappeared during the following days. On the seventh post-operative day, median pain ratings during deep inspiration were 0 (range: 0–2) in group SL and 1.5 (range: 0–3) in group SH (*p* = 0.16). There were no differences between the two groups with respect to pain ratings at rest. On post-operative days 0, 1 and 2, these were 0.8 ± 1.2, 2.3 ± 1.2 and 1.2 ± 1.4 in group SL, and 1.5 ± 1.4, 2.3 ± 1.4 and 1.9 ± 1.1 in group SH (*p* = 0.21).

3.3 Primary hyperalgesia

When compared with baseline, the stimulus-response curves were shifted to the left on the first 3–4 post-operative days with the maximum shift observed on the second and third post-operative day (Figs 2 and 3). Whereas the time effect was significant (*p* = 0.039), there was no significant difference between the two groups (*p* = 0.88). The area between the stimulus-response curves was significantly different from zero on the second and/or third post-operative day (Fig. 3), indicating primary hyperalgesia.

3.4 Secondary hyperalgesia

The extent of secondary mechanical pinprick hyperalgesia as assessed by the distance between the bound-

ary of the hyperalgesic area and the sternotomy wound increased during the first 2–3 post-operative days and decreased subsequently (Fig 4). Whereas this time effect was significant ($p < 0.01$), there was no significant difference between the two groups ($p = 0.09$).

3.5 Side effects

At baseline, all patients showed a normal cognitive function with median mini-mental score values of 29.5 (range: 27–30) in group SL and 29 (range: 25–30) in group SH. On the first post-operative day, we observed a small but significant decrease to 27 (range: 20–30) in group SL ($p < 0.01$) and to 27 (range: 18–30) in group SH ($p < 0.05$). On the following post-operative days, the mini-mental score values were not different to baseline. There were no significant differences between the groups. The main side effects of the analgesic regimen were constipation and PONV. These side effects were most prominent on the first two

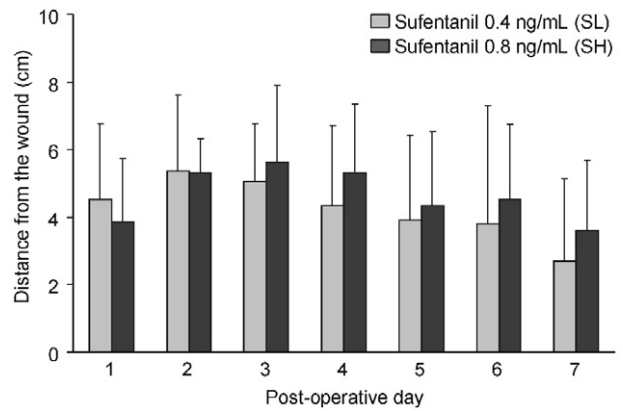


Figure 4 Extent of secondary pinprick hyperalgesia as measured by the distance between the boundary of the hyperalgesic area and the sternotomy wound. Data are expressed as mean \pm SD. SH, high sufentanil target group; SL, low sufentanil target group.

post-operative days, when the incidence of constipation and PONV was 93% and 10% in group SL, and 96% and 12% in group SH, respectively. On the following days, these side effects disappeared. There were no significant differences between the groups.

4. Discussion

We studied the effect of low and high intra-operative doses of sufentanil on post-operative opioid consumption, pain and hyperalgesia in patients with CABG surgery from the preoperative day to the seventh day post-operatively. Primary endpoints were the cumulative post-operative morphine consumption, the pain rating during deep inspiration, the primary hyperalgesia as assessed by the area between the stimulus response curves and the extent of secondary mechanical pinprick hyperalgesia. We found a significant influence of the intra-operative sufentanil dosing on the morphine consumption, which was higher in the high dose group, and also on the pain rating, which was lower in the low sufentanil dose group on the day of surgery. Primary and secondary hyperalgesia was observed in all patients with the maximum on the second and third post-operative day without significant differences between the two sufentanil dosing groups.

There is an ongoing debate about opioid-induced hyperalgesia since a higher post-operative morphine consumption after high intra-operative dosing of remifentanyl was reported by Guignard et al. (2000). Such an increase of post-operative morphine consumption was also observed in the present study, as the patients in the high target group requested more morphine than those in the low target group. This

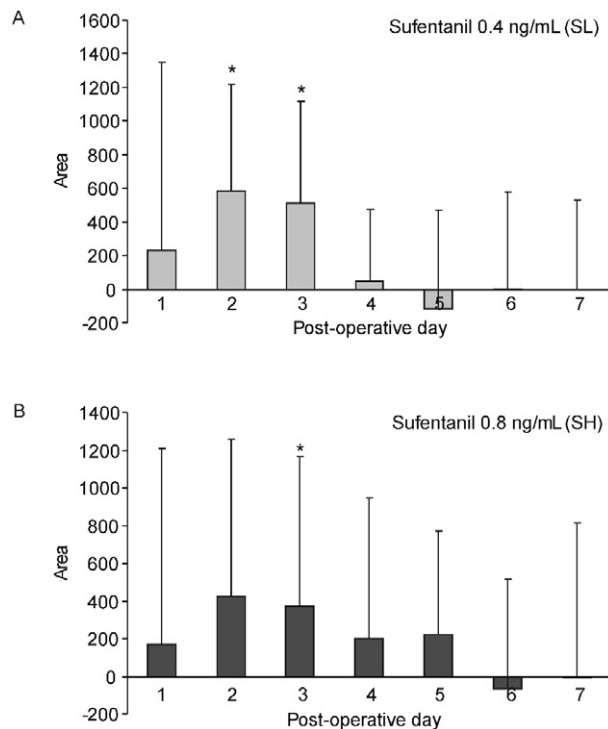


Figure 3 Extent of primary hyperalgesia as measured by the area between the stimulus-response curves at baseline and at the respective post-operative day. A positive value means a left shift of the stimulus-response curve, and a negative value a right shift of the stimulus-response curve compared to baseline. Data are expressed as mean \pm SD. SH, high sufentanil target group; SL, low sufentanil target group. *Area significantly different from zero ($p < 0.05$).

finding indicates therefore some kind of tolerance or hyperalgesia after sufentanil administration. An increase of the required dose, i.e., a right shift of the dose–effect relationship, is usually interpreted as a sign of tolerance or desensitization of antinociceptive pathways, whereas a downshift of the dose–effect relationship indicates hyperalgesia or sensitization of pronociceptive pathways (Angst and Clark, 2006). It is, however, hard to discriminate these two phenomena if only dose requirements have been determined. Therefore, it is appropriate to look also at the stimulus-response curves and not only at the dose requirements. In this view, primary hyperalgesia is characterized by a left-shift, so that the same stimulus causes an increased pain sensation (Sandkühler, 2009). This primary hyperalgesia was observed in both of our study groups on the second and third post-operative day (Fig 3), but without any significant differences between the treatments, and this left shift also disappeared during the next post-operative days. One has, however, to consider that the stimulus-response data were censored as no analgesic medication was present at baseline, whereas the post-operative data were collected under analgesic treatment. Therefore, it is not clear, whether the observed primary hyperalgesia was simply caused by the tissue damage at the sternotomy wound or whether it was also in part induced by the intra-operative administration of sufentanil and/or the post-operative administration of morphine itself.

The pain during deep inspiration was smaller in the low dose group on the day of surgery, and the smaller morphine PCA requirement in this group is in accordance with this finding. In the first few hours between admission at ICU and extubation, the total doses of opioids, including piritramide, were not different between the two groups, so that one can assume that the condition at start of the PCA was similar for all studied patients. As the patients were not instructed to target a specific pain rating under deep inspiration, the PCA dosing may have been mainly driven by the pain at rest, which was permanently present. As the pain at rest was relatively small (NRS around 2) and not different between the groups, one may conclude that the pain at rest was successfully treated by the PCA, whereas the testing of the pain under inspiration uncovered some differences. The observation that the difference between the two groups vanished in the following days may also be interpreted in that way that the PCA with morphine was able to provide sufficient analgesia in both groups.

With regard to secondary mechanical pinprick hyperalgesia, there was a significant trend over time

but no differences between the two dosing groups. Opioid-induced secondary hyperalgesia was seen for remifentanil in a volunteer study with an experimental pain model (Koppert et al., 2003), where the extent of the hyperalgesic area for the same stimulus was larger after remifentanil administration than at baseline. In this study, hyperalgesia was induced by electrical stimulation and was present already before drug administration. In patient studies, however, one cannot induce secondary hyperalgesia before surgery. One should further consider that induction of pain by electrical stimulation and surgically induced pain with its tissue trauma cannot be directly compared. One may discuss, whether the shift of the stimulus-response curves (Fig. 3) may also be attributed to secondary hyperalgesia as it is not completely clear where the surgical tissue damage ends, which makes it difficult to clearly distinguish primary and secondary hyperalgesia.

Altogether, the findings that pain at rest, primary and secondary hyperalgesia were not different between the two sufentanil groups, but that the high dose group requested more morphine may interpret such that the high intra-operative sufentanil dose induced hyperalgesia, which was effectively treated with the PCA therapy.

Whereas opioid-induced hyperalgesia has been discussed extensively for remifentanil, there are very few studies about hyperalgesia after sufentanil. Devulder reported a single case of sufentanil hyperalgesia in a patient suffering from neuropathic pain (Devulder, 1997). In animal studies, Freye and Levy (2010) and Minville et al. (2010) reported hyperalgesia following sufentanil administration. In our study, primary hyperalgesia occurred in both sufentanil groups but without significant differences. The major findings were the smaller post-operative opioid consumption and the lower pain under deep inspiration after low dose sufentanil compared to high dose sufentanil.

Both sufentanil groups were similar with regard to the major side effects PONV and constipation, and also with respect to the transient post-operative impairment of the cognitive function. From the results of this study, one may conclude that, in combination with propofol, a target concentration of 0.4 ng/mL sufentanil may be preferable for cardiac surgery. For fast-track cardiac anaesthesia, Lison et al. found also better performance in the post-operative phase after sufentanil compared to remifentanil (Lison et al., 2007). An earlier study by Engoren et al. did not find any significant differences between sufentanil and remifentanil for fast-track anaesthesia (Engoren et al., 2001). In studies comparing remifentanil and sufentanil during

non-cardiac surgery, it was found also that the use of sufentanil resulted in slower awakening but less requirement of post-operative analgesics (Gerlach et al., 2003; Martorano et al., 2008; Bidgoli et al., 2011).

There are limitations of the study. The sample size allowed us to detect only distinct differences between the groups. The present findings may be valid only for the combination of sufentanil with propofol. An effect of propofol was discussed with regard to remifentanil-induced hyperalgesia (Singler et al., 2007), but we cannot say anything about the role of propofol with regard to sufentanil-induced pain and hyperalgesia because propofol doses and BIS values were not different between groups in this study. Another limitation is the lack of long-term evaluation to detect development of post-operative chronic pain. In a recent study, it was reported that a high dose of remifentanil was required to blunt the memory of pain in the spinal cord (Drdla-Schutting et al., 2012). Therefore, high dose of opioids may produce immediate hyperalgesia but may well counteract long-term chronic pain development. This should be investigated in further studies.

In conclusion, intra-operative sufentanil dosing significantly influenced post-operative morphine consumption, pain and hyperalgesia. During cardiac anaesthesia with propofol, a sufentanil target plasma concentration of 0.40 ng/mL may be preferable.

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Author contributions

J. Fechner: conception and design of the study, data acquisition, data interpretation, drafting and revising of the article, final approval.

H. Ihmsen: conception and design of the study, data analysis, data interpretation, drafting and revising of the article, final approval.

J. Schüttler: conception and design of the study, data interpretation, revising of the article, final approval.

C. Jeleazcov: conception and design of the study, data acquisition, data analysis, data interpretation, drafting and revising of the article, final approval.

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