ORIGINAL ARTICLE

Randomized Controlled Trial on the Influence of Intraoperative Remifentanil versus Fentanyl on Acute and Chronic Pain after Cardiac Surgery

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■ **Abstract**

Background: Remifentanil has been associated with increased acute and potentially chronic postoperative pain. The objective of this prospective randomized controlled trial was to investigate the influence of intraoperative remifentanil on acute and chronic postoperative pain after cardiac surgery.
Methods: Patients (N = 126) receiving standardized anesthesia with propofol and intermittent intravenous fentanyl at predetermined times for cardiac surgery were randomized to intraoperatively receive either a continuous remifentanil infusion or additional intermittent intraoperative fentanyl as needed. The primary endpoint was chronic thoracic pain at 12 months after surgery. Secondary endpoints were pain at 3 and 6 months after surgery and analgesic requirements and pain levels in the first 72 hours.
Results: There was no significant difference in incidence of chronic thoracic pain between the remifentanil and fentanyl groups, respectively (20% vs. 18%; P = 0.817). At 3 months, however, significantly more patients in the remifentanil group reported chronic thoracic pain (51% vs. 33%; P = 0.047). This effect was more pronounced in younger patients and in patients receiving a higher dose of remifentanil (both $P < 0.05$). The first 24 and 48 hours postoperatively, morphine consumption in the remifentanil group was significantly higher than in the fentanyl group (34.3 mg [interquartile range (IQR) 25.3 to 48.2] vs. 30.2 mg [IQR 19.2 to 38.1], P = 0.028; and 46.8 mg [IQR 33.8 to 59.2] vs. 39.0 mg [IQR 6.2 to 51.4], P = 0.047, respectively).
Conclusions: Intraoperative use of remifentanil during cardiac surgery does not impact chronic postoperative pain 1 year after surgery. Nevertheless, remifentanil increases analgesic requirements and thoracic pain until 3 months after surgery, and its use is therefore less favorable during cardiac surgery. ■

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INTRODUCTION

Opioids are part of the multimodal anesthesia regimen for the management of pain during and after surgery. One of these opioids, remifentanil, is often used because of its favorable pharmacokinetic and pharmacodynamic properties, including fast onset and offset of action, predictable rapid recovery profile independent of infusion duration, and metabolism independent of kidney or liver function.[1,2]

Recently, however, opioids, and remifentanil in particular, have been associated with opioid-induced hyperalgesia, or acute opioid tolerance.[1,3] Concerning remifentanil, its ultra-short half-life, resulting in abrupt analgesic offset after cessation of the infusion, is thought to contribute to high postoperative pain levels.[1] Still, the clinical impact of these higher levels in the short term, but particularly in the long term, is not clear.[4–6.]

In recent years, more attention has been focused on the risk for chronic pain after surgery.[7,8] The International Association for the Study of Pain defines chronic postoperative pain as pain that develops after surgical intervention and lasts at least 2 months while other causes of pain have been excluded.[9] Specifically for cardiac surgery, where the incidence of chronic postoperative pain is relatively high,[10] intraoperative use of remifentanil has been associated with chronic thoracic pain.[11,12] In a randomized study designed to evaluate the occurrence of chronic thoracic pain after cardiac surgery, remifentanil was combined with epidural anesthesia. The incidence of chronic pain in the high-dose remifentanil group was significantly higher than in the low-dose group.[12] In another observational study in 90 cardiac surgery patients, intraoperative remifentanil was predictive for chronic thoracic pain in a dose-dependent manner.[11] However, this study was not designed to investigate the role of remifentanil in chronic pain after surgery.

Therefore, we performed a prospective randomized controlled trial investigating the influence of intraoperative remifentanil administration during cardiac surgery on the development chronic thoracic pain after surgery. For this purpose, we randomized between 2 standard care regimens in our hospital and collected data on chronic postoperative pain and quality of life 3, 6, and 12 months after surgery. In addition, acute pain was evaluated by collecting pain scores and morphine consumption over the first 72 postoperative hours.

METHODS

Design and Patients

This study is a prospective, randomized, single-blind clinical trial of which the study protocol has been published previously.[13] The study was approved by the local research ethics committee and registered at ClinicalTrials.gov (NCT02031016). Patients were included from February until November 2014. Written informed consent was obtained from all subjects. Eligible patients were randomly assigned 1:1 (using computerized random numbers) to either the remifentanil or the fentanyl study arm and blinded for treatment group allocation. Inclusion criteria were: (1) patients undergoing cardiac surgery via sternotomy (a coronary artery bypass graft and/or valve replacement); (2) age between 18 and 85 years; and (3) weight between 45 and 140 kg. Exclusion criteria were: (1) pregnancy or breastfeeding; (2) language barrier; (3) history of drug abuse; (4) neurologic condition such as peripheral neuropathy or fibromyalgia; (5) known remifentanil, fentanyl, morphine, or paracetamol allergy; (6) body mass index above 35 kg/m^2; (7) prior cardiac surgery (reoperations); or (8) chronic pain condition.

Intraoperative Anesthesia and Analgesia

Premedication and induction of anesthesia were standardized in all patients. Both groups then received a continuous infusion of propofol (starting dose 200 to 300 mg/hour) and intermittent intravenous fentanyl (500 μg) at predetermined times (ie, before incision, at sternotomy, at aorta cannulation, and at opening of the pericardium). At the discretion of the attending anesthesiologist, the dose of fentanyl could be reduced to a minimum of 200 μg depending on patient characteristics (eg, old age, hemodynamics, low body weight, ejection fraction). Patients in the remifentanil group received a continuous infusion of remifentanil (starting dose 0.15 μg/kg/ideal body weight/minute) in addition to the propofol and predetermined fentanyl anesthetic regimen. The remifentanil starting dose could be adjusted at the discretion of the anesthesiologist. Patients in the fentanyl group received additional

boluses of fentanyl if predetermined fentanyl doses were insufficient. The attending anesthesiologist decided, based on patient characteristics (eg, sweating, hemodynamics, body weight, ejection fraction), if extra fentanyl (200 to 500 μg) was indicated. In both groups, sevoflurane was used as needed, and no nitrous oxide was used. In both groups, patients received 5 or 10 mg of intravenous morphine (depending on hemodynamic status) 30 minutes before the anticipated end of surgery.

Postoperative Pain Measurement and Analgesia

After surgery, patients were first admitted either to the intensive care unit (ICU) or postanesthesia care unit (PACU). These units and the general postoperative ward use the same standardized postoperative treatment.[14,15] Numeric rating scale (NRS) pain scores (0 to 10) were collected at least 3 times a day by the nursing staff on the ICU/PACU or ward. Immediately after surgery, 1 g of oral or intravenous paracetamol was given 4 times a day together with a continuous infusion of morphine (starting dose 2 mg/hour), which was adapted individually on the guidance of the patient's NRS pain scores. A pain titration protocol was used, with a targeted NRS value of < 4. Analgesics were increased after patients reported an NRS score of ≥ 4 and decreased after patients reported an NRS score of 0 or 1.[15] The continuous infusion of morphine was stopped upon transfer to the general postoperative ward and replaced by 2.5 to 10 mg of (intravenous) morphine on demand. Paracetamol (1 g oral or intravenous) 4 times a day was continued until discharge. On the ward, patients could receive oxycodone or tramadol orally, which was calculated to morphine equivalents. Consumption of opioids was calculated per 24 hours until 72 hours after surgery.

Study Endpoints

The primary endpoint of this study was chronic postoperative pain, which was evaluated at 12 months after cardiac surgery. Chronic thoracic pain was defined as sternal and/or thoracic pain (NRS score > 0) that the patient identified as related to surgery and that was different from angina.[16] Chronic thoracic pain was measured with a questionnaire based on the Brief Pain Inventory[17] and described previously.[16] The questionnaire was sent by regular mail or e-mail. Secondary outcomes were chronic pain at 3 and 6 months after surgery, opioid consumption during the first 72 hours after surgery, and health-related quality of life at 3, 6, and 12 months after surgery.

Quality of life was measured using the physical composite score (PCS) and the mental composite score (MCS) of the short form (SF)-12 health status instrument, both ranging from 0 to 100, with higher scores representing higher levels of functioning.[18] Dutch age- and sex-standardized population norms are available elsewhere.[19.]

Statistical Analysis

The planned statistical analyses have been described previously.[13] We determined that a sample size of 126 patients would provide a power of 80% to detect a 20% absolute reduction in the primary outcome from a baseline risk of 30%, at a 2-sided alpha level of 0.05.[11] All analyses were performed according to the intention-to-treat principle. We used the chi-square test or Fisher's exact test to analyze categorical variables and Student's *t*-test or the Mann-Whitney test for continuous variables. The Kolmogorov-Smirnov test together with visual inspection of the histograms were used to assess whether the variables were normally distributed. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to quantify risk. Imbalance (if any) in the baseline characteristics was approached from a clinician's and literature perspective and statistically tested through assessment of the impact on the coefficient of the treatment allocation in a multivariable logistic regression analysis. Post hoc, we have also explored (1) the potential effect modification by testing the significance of an interaction term with age in our multivariable logistic regression model and (2) a potential dose-related effect of remifentanil by replacing the dichotomous treatment allocation variable by a categorical variable (fentanyl, low-dose remifentanil, high-dose remifentanil). A sensitivity analysis was conducted by exclusion of patients with missing data at any of the intermediate follow-up time points. The statistical analyses were conducted with the SPSS statistical package (version 24.0 for Windows; SPSS, Chicago, IL, U.S.A.). All statistical tests were 2-sided and used a significance level of 0.05.

RESULTS

Figure 1 shows the randomization and flow of patients in the trial; of the 555 patients screened for eligibility, 128 patients signed informed consent, of which 2 were

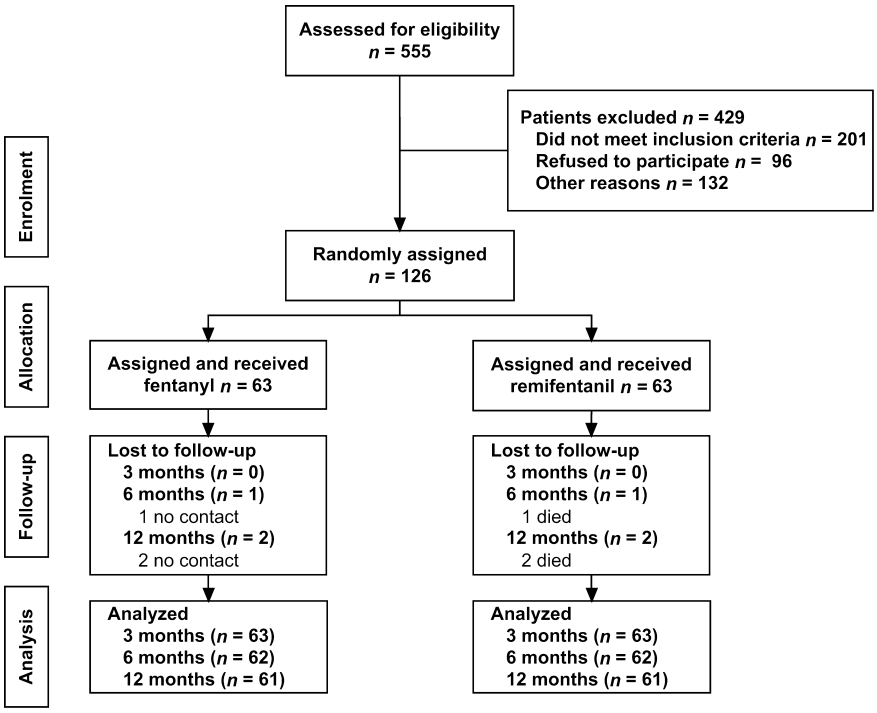

Figure 1. Consort diagram with the flow of the patients in the study.

excluded later because of the exclusion criteria (1 patient's surgical procedure was altered to a noninvasive approach and 1 patient appeared to have had prior cardiac surgery). Table 1 describes the characteristics of the remaining 126 patients. A total of 122 patients (96.8%) filled out the questionnaire 12 months after the study; 2 patients died, and contact was lost with 2 other patients. All analyses for the primary outcome were based on the data from these 122 patients.

Outcomes

The primary outcome, chronic thoracic pain 12 months after surgery, was not significantly different between the remifentanil and fentanyl groups, respectively (20% vs. 18%; $P = 0.817$; OR 0.9; 95% CI 0.4 to 2.2) (Table 2). Regarding physical and mental composite scores of quality of life 1 year after surgery (secondary outcome), no differences between the remifentanil and fentanyl groups, respectively, were found (PCS 57.0 [interquartile range (IQR) 53.3 to 59.6] vs. 56.9 [IQR 51.2 to 58.8], $P = 0.459$; MCS 55.2 [IQR 50.7 to 58.1] vs. 55.7 [IQR 52.2 to 58.6], $P = 0.596$) (see Table 2). In the group of 23 patients who reported pain 12 months after surgery, pain levels were not significantly different between the remifentanil and fentanyl groups, respectively, on an average day (4.0 [IQR 2.0 to 4.0] vs. 3.0 [IQR 1.3 to 5.8]; $P = 0.708$), good day (2.0 [IQR 1.0 to 4.0] vs. (0.0 [IQR 0.0 to 3.0]; $P = 0.113$), or bad day (5.0 [IQR 2.0 to 7.0] vs. 3.5 [IQR 1.3 to 5.8]; $P = 0.226$). Type of pain was comparable between the remifentanil and fentanyl groups, respectively, and was mostly described as sharp pain (36.4% vs. 41.7%) or pressure pain (36.4% vs. 33.3%). Pain was mostly localized around the site of incision in both the remifentanil group and the fentanyl group, respectively (63.6% vs. 41.7%; $P = 0.524$). No significant differences were found between pain characteristics at different time points (see Table S1 in the Supplementary Appendix).

Figure 2 shows the percentage of patients reporting thoracic pain after 3, 6, and 12 months. The proportion of patients reporting thoracic pain after 3 months was significantly higher in the remifentanil compared to the fentanyl group, respectively (51% vs. 33%; $P = 0.047$; OR 2.1; 95% CI 1.0 to 4.2). The effect was not different at 6 months (32% vs. 27%; $P = 0.556$; OR 0.8; 95% CI 0.4 to 1.7).

During the first 24 and 48 hours after surgery, the median consumption of opioids in the remifentanil group was significantly higher than in the fentanyl group, respectively (34.3 mg [IQR 25.3 to 48.2] vs. 30.2 mg [IQR 19.2 to 38.1], $P = 0.028$; and 46.8 mg [IQR 33.8 to 59.2] vs. 39.0 mg [IQR 26.2 to 51.4], $P = 0.047$) (Figure 3). This cumulative difference in opioid consumption was not significantly different at

Table 1. Characteristics of Patients in the Remifentanil and Fentanyl Groups

	Fentanyl (n = 63)	Remifentanil (n = 63)
Male gender	57 (90%)	58 (92%)
Age (years)	66 (7.6)	62 (9.0)
BMI (kg/m^2)	28.0 (3.1)	27.5 (3.6)
Preoperative NRS score	0 (0 to 0)	0 (0 to 0)
Preoperative quality of life score		
PCS	49.3 (43.3 to 53.1)	47.6 (39.6 to 54.3)
MCS	51.3 (46.1 to 57.2)	50.4 (46.8 to 54.3)
Type of surgery		
CABG	51 (81%)	49 (78%)
Valve	9 (14%)	7 (11%)
Combination	3 (5%)	7 (11%)
euroSCORE	3 (2 to 4)	2 (0 to 4)
Duration of anesthesia (minutes)	218.6 (49.0)	233.4 (72.1)
Duration of surgery (minutes)	187.4 (46.7)	198.1 (70.8)
Mechanical ventilation (hours)	10.8 (4.5)	13.3 (23.8)
Intraoperative use of analgesics/sedatives		
Sevoflurane		
Minutes	32.8 (23.1)	32.4 (24.8)
MAC	0.34 (0.1)	0.33 (0.1)
End tidal	0.69 (0.3)	0.67 (0.3)
Propofol (mg/kg)	13.1 (4.4)	13.3 (6.9)
Fentanyl (μg/kg)	26.1 (9.0)	21.8 (7.8)
Remifentanil (μg/kg)	NA	25.1 (8.9)
Total remifentanil (μg)	NA	2165.0 (696.0)
Patients admitted to PACU	35 (56%)	41 (65%)
Length of hospital stay (days)	5.0 (3.0 to 7.0)	5.0 (3.0 to 7.0)
Length of stay in the ICU/PACU (hours)	19.5 (16.7 to 22.4)	19.6 (16.2 to 21.4)

Continuous data are presented as means (standard deviation) or medians (interquartile range), and categorical data are presented as number (%).
BMI, body mass index; CABG, coronary artery bypass grafting; MAC; minimum alveolar concentration; NRS, numeric rating scale; IQR, interquartile range; PCS, physical composite score; MCS, mental composite score; PACU, postanesthesia care unit; ICU, intensive care unit.

72 hours after surgery (48.3 mg [IQR 34.7 to 62.2] vs. 43.0 mg [IQR 27.9 to 76.3]; P = 0.162). This difference in opioid consumption led to no significant difference

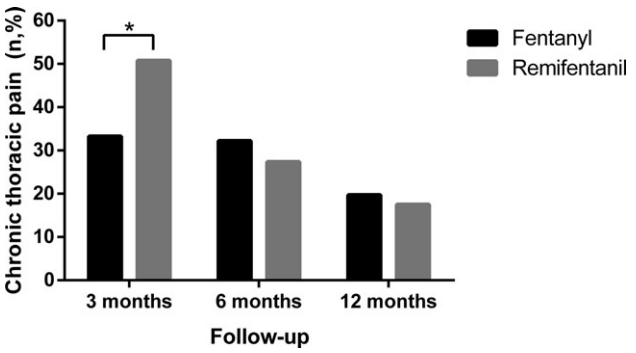

Figure 2. Chronic postoperative pain reported 3, 6, and 12 months after surgery in the fentanyl group (solid black) compared to the remifentanil group (grey). *P = 0.047.

(P > 0.05) in pain scores (NRS) the first 72 hours after surgery (see Table S2 in the Supplementary Appendix). There was no significant difference between the amount of morphine given at the anticipated end of surgery (10.0 mg [IQR 10.0 to 10.0] vs. 10.0 [IQR 10.0 to 10.0]; P = 0.953).

Because there was a 4-year difference in mean age (66 years vs. 62 years, P = 0.007) between the remifentanil and fentanyl groups, respectively, we explored the impact of imbalanced age in a multivariable logistic regression analysis. In that analysis, age altered the coefficient of treatment allocation by more than 10%, resulting in an adjusted OR of 0.6 (95% CI 0.2 to 1.7; P = 0.362).

In a post hoc analysis, effect modification by age was not significant 12 months after surgery. No significant difference of chronic pain 12 months after surgery was found between patients < 65 years of age (adjusted OR 1.1; 95% CI 0.3 to 3.7; P = 0.920) and patients ≥65 years of age (adjusted OR 0.4; 95% CI 0.1 to 2.1;

Table 2. Chronic Thoracic Pain and Quality of Life at 3, 6, and 12 Months

	Fentanyl	Remifentanil	RR (95% CI)	P Value
Chronic thoracic pain (n, %)				
3 months (n = 126)	21 (33%)	32 (51%)	2.1 (1.0 to 4.2)	0.047
6 months (n = 124)	20 (32%)	17 (27%)	0.8 (0.4 to 1.7)	0.556
12 months (n = 122)	12 (20%)	11 (18%)	0.9 (0.4 to 2.2)	0.817
Quality of life (median, IQR)				
3 months (n = 126)				
PCS	55.0 (46.9 to 58.3)	55.4 (49.3 to 58.8)		0.971
MCS	51.4 (47.9 to 55.6)	54.0 (48.7 to 57.4)		0.325
6 months (n = 124)				
PCS	56.0 (50.4 to 58.1)	55.9 (48.5 to 58.8)		0.901
MCS	53.2 (49.3 to 57.5)	54.4 (49.3 to 57.4)		1.0
12 months (n = 122)				
PCS	56.9 (51.2 to 58.8)	57.0 (53.3 to 59.6)		0.459
MCS	55.7 (52.2 to 58.6)	55.2 (50.7 to 58.1)		0.596

Continuous data are expressed as means (standard deviation) or medians (interquartile range), and categorical data are expressed as number (%).
95% CI, 95% confidence interval; IQR, interquartile range; NRS, numeric rating scale; MCS, mental composite score; PCS, physical composite score.

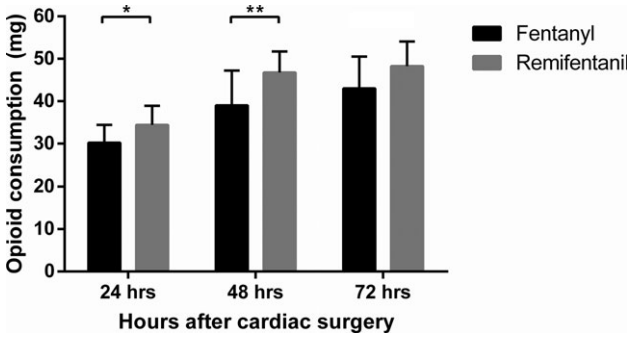

Figure 3. Cumulative opioid consumption 24, 48, and 72 hours postoperatively in the fentanyl group (solid black) compared to the remifentanil group (grey). *P = 0.028; **P = 0.047.

P = 0.281). No dose-related effect of remifentanil on chronic pain 12 months after surgery was found. Regarding the secondary endpoints, age was found to be an effect modifier through an interaction term (P = 0.052). This resulted in a significant effect of remifentanil on chronic thoracic pain after 3 months for patients < 65 years of age (adjusted OR 4.0; 95% CI 1.3 to 12.2; P = 0.016) and no effect in patients ≥65 years of age (adjusted OR 0.9; 95% CI 0.3 to 2.5; P = 0.856). This effect of age was absent 6 months after surgery. A dose-related effect of remifentanil on pain after 3 months with ORs of 1.3 (95% 0.5 to 3.1) and 3.3 (95% CI 1.4 to 8.1) was also observed for a cumulative dose of < 1,875 μg and ≥ 1,875 μg, respectively. This dose-related effect was absent for the outcome of chronic pain 6 months after surgery. The sensitivity analysis excluding patients with missing data at any of the time points resulted in very similar results compared to the original analyses (see Table S3 in the Supplementary Appendix).

DISCUSSION

This randomized single-blind controlled trial showed that the use of remifentanil during cardiac surgery does not lead to an increased incidence of chronic thoracic pain 12 months after surgery. Considering the short-term effects, remifentanil was associated with a small, but significant, increase in postoperative opioid consumption during the first 48 hours after cardiac surgery. In addition, more patients in the remifentanil group developed chronic thoracic pain at the site of surgery after 3 months, and this effect proved to be age dependent and dose related.

To start, this study showed no significant increase in chronic thoracic pain 12 months postoperatively for remifentanil compared to fentanyl, even though a significant difference in reported thoracic pain was observed 3 months after surgery (see Figure 2). The latter suggests alteration of pain sensitivity caused by remifentanil. Our finding that chronic pain was especially observed in patients receiving a higher dose of remifentanil further supports this. A dose-dependent relationship is also in line with previous reports.[11,20,21]

A few other studies have suggested an effect of remifentanil on chronic pain. Salengros et al.[12] concluded that high-dose remifentanil plus postsurgical epidural analgesics resulted in higher incidences of chronic pain after cardiac surgery compared to preoperative epidural analgesics and low-dose remifentanil during surgery. In another observational, nonrandomized study, remifentanil proved to be a risk factor for the development of chronic pain at 12 months in a dose-dependent manner.[11] In contrast to our study, these studies were not designed to measure the effect of remifentanil on chronic postoperative pain and/or postoperative analgesics.

Generally stated, the mechanisms of postprocedural pain and chronic postsurgical pain are complex and poorly understood. Nerve injury or inflammatory reactions after surgery causing central sensitization are suggested as causes of postsurgical pain.[22] Modulation or increased activity of N-methyl-D-aspartate (NDMA) receptors have been hypothesized to lead to inflammatory and neuropathic pain states,[23] and possibly activation and exacerbation of hyperalgesia.[24] It is known that remifentanil affects the NMDA receptor directly or indirectly,[23,25] which as such could influence the development of acute and chronic pain. This effect of remifentanil on the NMDA receptor could explain the higher morphine consumption immediately postsurgery and the higher incidence of chronic thoracic pain after 3 months in the remifentanil group. In addition, age-related alterations of NMDA receptors[26,27] and decreased neuroplasticity in the elderly could explain the relatively lower sensitivity to the effects of remifentanil at higher age, found in this study. This finding requires further exploration as this subgroup analysis was not predefined.

In this study we quantified acute postoperative pain on the basis of the need for postoperative opioids in the first 72 hours, as was done in previous studies.[3,4,28,29] All patients received, besides a morphine loading dose on the operating room at the end of surgery, a continuous morphine infusion that was subsequently adapted on the guidance of individual pain scores. The

ICU and PACU in our hospital were the settings for this study, with a pain management protocol that has been in place for years[14] allowing for randomized controlled trials and related studies.[15,30,31] In this setting, patients receiving intraoperative remifentanil received significantly more morphine after 48 hours postsurgery compared to patients receiving intraoperative fentanyl, which implies that patients in the remifentanil group requested more pain relief. While the difference between the groups is statistically significant, the absolute difference is very small and most likely not of clinical consequence as there are no safety issues involved with these amounts of morphine. Still, other studies have also reported an association between the administration of intraoperative remifentanil and an increase in consumption of postoperative analgesics during the first 24 or 48 postoperative hours.[20,21,32–34] Compared to these reports, our study was the first randomized controlled trial that also investigated and reported chronic thoracic pain.

In times of cost containment in health care, remifentanil has, due to its favorable pharmacokinetic profile, received special interest in fast-track cardiac surgery. The use of remifentanil potentially reduces the time on mechanical ventilation and length of hospital stay.[35] However, when reviewed from a patient point of view, the advantages of remifentanil are questionable. In addition to worse pain outcomes, postoperative cognitive dysfunction and recovery after fast-track surgery were not improved when remifentanil was compared to long-acting sufentanil.[36,37] In light of these results, clinicians should outweigh the proposed benefits of remifentanil against the suggested negative impact for the patients, such as the impact on postoperative pain, knowing that several alternatives for remifentanil are available and that a lower dose of remifentanil decreases the risk for development of chronic pain during the first couple of months. Cardiac surgery is major surgery with a high incidence of chronic postoperative pain; therefore, remifentanil may not be the ideal opioid for this kind of surgery.

Some limitations of our study should be addressed. First, as pointed out in our study protocol,[13] ideally, the study design should be double blind and contain no other opioid besides remifentanil. However, since patients themselves report postoperative pain scores, which in turn guide morphine administration, we felt that with blinding the patients only, adequate blinding for the main endpoint was already preserved. Moreover, a double-blind, double-dummy trial is not only labor intensive, but also expensive. In addition, a study arm without opioids is obviously unethical, and therefore we chose a design that had been described previously.[11] In this design, we decided not to compare fentanyl with a study arm with only short-acting remifentanil since it was expected that high doses of remifentanil would be needed in this painful and extended procedure. In our study, increased analgesic consumption in the remifentanil group was found, which was in accordance with other studies with different control groups,[20,21,38] although in those reports it could not be excluded that results were subject to selection bias. Last, sample size calculation was based on a reduction of the primary outcome from 30% to 10%, based on a previous observational study.[11] In our present study, the incidence of chronic postoperative pain was around 20% in both study arms, suggesting that other factors besides remifentanil might have been responsible for the increased risk for thoracic pain in the observational study. It might be possible that the calculated sample size for primary outcome may provide insufficient statistical power to detect clinically relevant differences on secondary outcome parameters such as pain scores.

In conclusion, remifentanil administration during cardiac surgery does not impact chronic postoperative pain 1 year after surgery. In the shorter term, remifentanil increases the need for opioid consumption postoperatively and leads to higher incidence of chronic thoracic pain 3 months after surgery. This negative impact in the shorter term makes remifentanil less favorable for prolonged surgery such as cardiac surgery.

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RESEARCH SUPPORT

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CONFLICT OF INTEREST

The authors state that they don't have any conflict of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of chronic pain.
Table S2. Acute postoperative pain levels.
Table S3. Sensitivity analyses ($N = 121$).

REFERENCES

1. Angst MS. Intraoperative use of remifentanil for TIVA: postoperative pain, acute tolerance, and opioid-induced hyperalgesia. *J Cardiothorac Vasc Anesth*. 2015;29(suppl 1): S16–S22.
2. Miller TE, Gan TJ. Total intravenous anesthesia and anesthetic outcomes. *J Cardiothorac Vasc Anesth*. 2015;29 (suppl 1):S11–S15.
3. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth*. 2014;112:991–1004.
4. de Hoogd S, Ahlers SJ, van Dongen EP, et al. Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature. *Clin J Pain*. 2016;32:726–735.
5. Yu EH, Tran DH, Lam SW, Irwin MG. Remifentanil tolerance and hyperalgesia: short-term gain, long-term pain? *Anaesthesia*. 2016;71:1347–1362.
6. Wilder-Smith OH, Arendt-Nielsen L. Postoperative hyperalgesia: its clinical importance and relevance. *Anesthesiology*. 2006;104:601–607.
7. Mansfield KE, Sim J, Jordan JL, Jordan KP. A systematic review and meta-analysis of the prevalence of chronic widespread pain in the general population. *Pain*. 2016;157:55–64.
8. Reddi D. Preventing chronic postoperative pain. *Anaesthesia*. 2016;71(suppl 1):64–71.
9. Macrae W, Davies H. Chronic postsurgical pain. In: Crombie IK, Linton S, Croft P, Von Korff M, LeResche L, eds. *Epidemiology of Pain*. Seattle, WA: IASP Press; 1999:125–142.
10. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth*. 2008;101:77–86.
11. van Gulik L, Ahlers SJ, van de Garde EM, et al. Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br J Anaesth*. 2012;109:616–622.
12. Salengros JC, Huybrechts I, Ducart A, et al. Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *J Cardiothorac Vasc Anesth*. 2010;24:608–616.
13. de Hoogd S, Ahlers SJ, van Dongen EP, Tibboel D, Dahan A, Knibbe CA. Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomized controlled trial. *Trials*. 2014;15:466.
14. van Gulik L, Ahlers SJ, Brkic Z, et al. Improved analgesia after the realisation of a pain management programme in ICU patients after cardiac surgery. *Eur J Anaesthesiol*. 2010;27:900–905.
15. Ahlers SJ, van Gulik L, van Dongen EP, et al. Efficacy of an intravenous bolus of morphine 2.5 versus morphine 7.5 mg for procedural pain relief in postoperative cardiothoracic patients in the intensive care unit: a randomised double-blind controlled trial. *Anaesth Intensive Care*. 2012;40:417–426.
16. van Gulik L, Janssen LI, Ahlers SJ, et al. Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur J Cardiothorac Surg*. 2011;40:1309–1313.
17. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23:129–138.
18. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–233.
19. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res*. 2009;18:403–414.
20. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology*. 2000;93:409–417.
21. Lee C, Kim YD, Kim JN. Antihyperalgesic effects of dexmedetomidine on high-dose remifentanil-induced hyperalgesia. *Korean J Anesthesiol*. 2013;64:301–307.
22. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367:1618–1625.
23. Li Y, Wang H, Xie K, et al. Inhibition of glycogen synthase kinase-3beta prevents remifentanil-induced hyperalgesia via regulating the expression and function of spinal N-methyl-D-aspartate receptors in vivo and vitro. *PLoS ONE*. 2013;8:e77790.
24. Voscopoulos C, Lema M. When does acute pain become chronic? *Br J Anaesth*. 2010;105(suppl 1):i69–i85.
25. Yuan Y, Wang JY, Yuan F, Xie KL, Yu YH, Wang GL. Glycogen synthase kinase-3beta contributes to remifentanil-induced postoperative hyperalgesia via regulating N-methyl-D-aspartate receptor trafficking. *Anesth Analg*. 2013;116:473–481.
26. Cohen SA, Muller WE. Age-related alterations of NMDA-receptor properties in the mouse forebrain: partial restoration by chronic phosphatidylserine treatment. *Brain Res*. 1992;584:174–180.
27. Wang C, Jensen FE. Age dependence of NMDA receptor involvement in epileptiform activity in rat hippocampal slices. *Epilepsy Res*. 1996;23:105–113.
28. Kim SH, Stoicea N, Soghomonyan S, Bergese SD. Intraoperative use of remifentanil and opioid induced

hyperalgesia/acute opioid tolerance: systematic review. *Front Pharmacol*. 2014;5:108.

29. Rivosecchi RM, Rice MJ, Smithburger PL, Buckley MS, Coons JC, Kane-Gill SL. An evidence based systematic review of remifentanil associated opioid-induced hyperalgesia. *Expert Opin Drug Saf*. 2014;13:587–603.

30. Ahlers SJ, Elens LL, van Gulik L, et al. The Val158Met polymorphism of the COMT gene is associated with increased pain sensitivity in morphine-treated patients undergoing a painful procedure after cardiac surgery. *Br J Clin Pharmacol*. 2013;75:1506–1515.

31. Ahlers SJ, Valitalo PA, Peeters MY, et al. Morphine glucuronidation and elimination in intensive care patients: a comparison with healthy volunteers. *Anesth Analg*. 2015;121:1261–1273.

32. Lee C, Lee HW, Kim JN. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparoendoscopic single-site urologic surgery. *Korean J Anesthesiol*. 2013;64:19–24.

33. Fukunaga AF, Alexander GE, Stark CW. Characterization of the analgesic actions of adenosine: comparison of adenosine and remifentanil infusions in patients undergoing major surgical procedures. *Pain*. 2003;101:129–138.

34. Lee C, Song YK, Jeong HM, Park SN. The effects of magnesium sulfate infiltration on perioperative opioid consumption and opioid-induced hyperalgesia in patients undergoing robot-assisted laparoscopic prostatectomy with remifentanil-based anesthesia. *Korean J Anesthesiol*. 2011;61:244–250.

35. Greco M, Landoni G, Biondi-Zoccai G, et al. Remifentanil in cardiac surgery: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth*. 2012;26:110–116.

36. Rasmussen LA, Ryhammer PK, Greisen J, Bhavsar RR, Lorentzen AG, Jakobsen CJ. Ultrashort acting remifentanil is not superior to long-acting sufentanil in preserving cognitive function—a randomized study. *J Clin Anesth*. 2016;33:127–134.

37. Bhavsar R, Ryhammer PK, Greisen J, Rasmussen LA, Jakobsen CJ. Remifentanil compared with sufentanil does not enhance fast-track possibilities in cardiac surgery—a randomized study. *J Cardiothorac Vasc Anesth*. 2016;30:1212–1220.

38. Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology*. 2005;103:147–155.