Does it still hurt? Perioperative opioid analgesia in different patient populations

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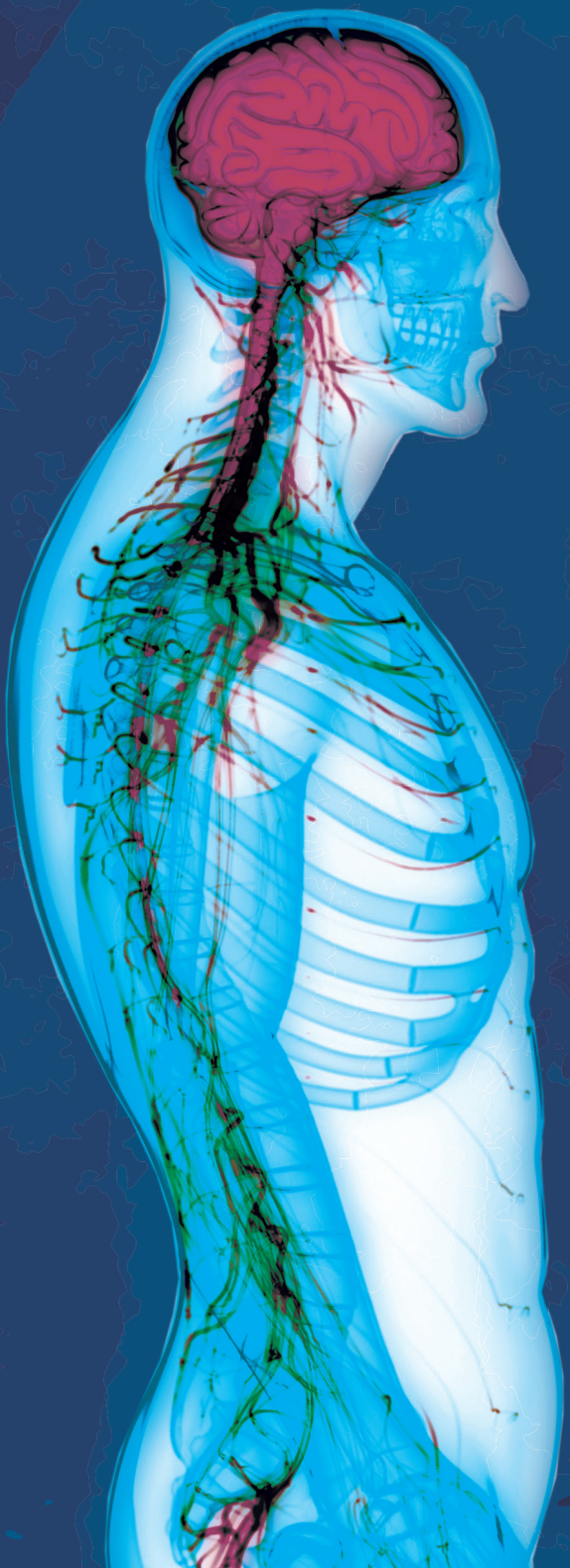

Section II

Opioid analgesia for acute and chronic pain in adult cardiac surgery patients

Chapter 2

Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature

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Abstract

Objective

Remifentanil is an ultra-short acting opioid that is commonly used during both short-term and prolonged surgery. This review investigated associations of intraoperative remifentanil administration with acute postoperative pain, hyperalgesia, and chronic postoperative pain, with emphasis on the perioperative coanaesthetic drug regimen used.

Methods

Medline and Embase databases were searched for randomized studies, evaluating the intraoperative use of remifentanil (>2 h) versus another analgesic or a different dosage of remifentanil, and reporting acute postoperative pain parameters like postoperative pain scores, hyperalgesia, acute opioid tolerance, or analgesics requirements. Furthermore, all studies in which remifentanil was used intraoperatively and parameters for chronic postoperative pain were measured were included (pain levels after a prolonged period of time after surgery).

Results

From the 21 studies that were identified, less than half of the studies found higher acute postoperative pain, higher postoperative analgesic requirements after intraoperative remifentanil use, or both. Coanaesthetics to some extent determined this incidence, with mainly studies using volatile agents reporting increased pain levels. There was less evidence when remifentanil was combined with total intravenous anaesthesia or a combination of anaesthetics. The limited number of studies (n = 4) evaluating chronic pain suggested a potential association with intraoperative use of remifentanil.

Discussion

While studies are divers and sample sizes small, coanaesthetics used in combination with remifentanil may influence the occurrence of postoperative hyperalgesia. No firm conclusions could be made regarding acute and chronic pain, indicating more research with the goal to investigate the effect of volatile or intravenous anaesthetics along with simultaneous remifentanil infusion on acute and chronic postoperative pain is needed.

Introduction

Moderate-to-severe acute postoperative pain is reported in 41% to 86% of the patients undergoing general surgery[1,2]. Acute postoperative pain is also a major risk factor for the development of chronic pain, that is, persistent pain at the surgical site 2 to 3 months after surgery[3–5]. The incidence of chronic postoperative pain varies from 5% to 65% upon different types of surgery and is known to influence health-related outcomes such as quality of life negatively by impairing performance of activities of daily living[6,7]. In view of the relevance of acute and chronic postoperative pain, medical institutions give increasing priority to asses and report patient-reported outcomes related to postoperative pain[8].

Intraoperative and postoperative administration of opioids is vital in preventing and treating postoperative pain. In contrast, the use of opioids may lead to phenomena such as acute opioid tolerance and opioid induced hyperalgesia (OIH)[9–12]. Although OIH was first thought to be associated with all opioids, the strongest association was found with remifentanil[13].

Remifentanil is an ultra-short-acting, hyperpotent, μ-opioid receptor agonist[14] and is often used for short-term and long-term surgery because of its favourable pharmacokinetic and pharmacodynamic properties, including rapid distribution throughout the body, rapid onset, a predictable rapid recovery profile, and dosing reliability[15]. Because remifentanil may directly or indirectly affect the N-methyl-D-aspartate (NMDA) receptor[13,16], it has been hypothesized that signalling of this NMDA receptor may lead to OIH[17]. When remifentanil is used in patients for intraoperative analgesia during surgery, it is coadministered with anaesthetics such as propofol, nitrous oxide, and/or volatile agents. As these anaesthetics may differ in their effect on the NMDA receptor[18,19], it seems of relevance to study the effect of remifentanil on hyperalgesia with respect to the coanaesthetics used[13]. Healthy volunteer studies, in which acute opioid tolerance and OIH has been described substantially, used different pain models and techniques to induce or to measure pain, hyperalgesia and tolerance[20–23]. Concerning hyperalgesia after opioid administration, a larger area of hyperalgesia or a decreased lower mechanical pain threshold has been reported, even though pain scores did not increase[21–25]. The relevance of these findings for clinical patients is unknown because the induced effect in healthy volunteers is restricted to a small region relative to the total body size, whereas patients may experience pain over a much larger area. Moreover, remifentanil infusion in healthy volunteers did not always lead to increased VAS pain scores, which also implies that the clinical implications of these findings for postoperative patients remain unclear[21,24,25].

The purpose of this review is therefore to give an update of the literature concerning the intraoperative use of remifentanil in relation to acute postoperative pain intensity, analgesic consumption, OIH or acute opioid tolerance, and chronic postoperative pain, with emphasis on the intraoperative coanaesthetic drug regimen used.

Materials and Methods

A literature search was performed in Medline (PubMed) and Embase databases using the term "remifentanil", combined with the following terms: "hyperalgesia", "postoperative pain", "opioid induced hyperalgesia", "tolerance" and "chronic pain". The detailed search strategy is available in Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/CJP/A333). Abstracts of retrieved citations were reviewed to identify whether inclusion and exclusion criteria were met.

For acute postoperative pain, clinical studies in surgical patients were included if (1) patients were randomized between the intraoperative use of remifentanil and another analgesic or a different dosage of remifentanil; (2) surgical time was longer than 120 minutes (or, if surgical time was not noted, anaesthesia time was >150 min); and (3) acute postoperative pain parameters (if available pain scores, hyperalgesia, acute opioid tolerance, or analgesics requirement) were evaluated. Clinical studies in surgical patients were excluded if (1) surgical or anaesthesia time was not given; (2) no full text was available or language was not English; (3) they were not original articles (e.g. editorials, letters to editors, poster abstracts, commentary); (4) remifentanil was used either preoperatively or postoperatively only or was combined with intraoperative use of intrathecal analgesics; or (5) they included patients younger than 18 years.

For chronic postoperative pain, all studies in which remifentanil was used intraoperatively in adults and pain levels were measured after a prolonged period of time after surgery (e.g. 3, 6 or 12 months postoperatively) were included, implying that studies where remifentanil was combined with intraoperative use of intrathecal analgesics are also reported.

Studies were categorized by the drug regimen used to maintain anaesthesia, that is, volatile agents, total intravenous anaesthesia (TIVA), or a combination of both. Outcomes of postoperative pain levels, analgesic requirements and measurements of hyperalgesia and opioid tolerance are discussed. Strategies to overcome possible remifentanil-induced hyperalgesia, such as the addition of NMDA antagonists, are reviewed elsewhere and are not in the scope of this article[10,12].

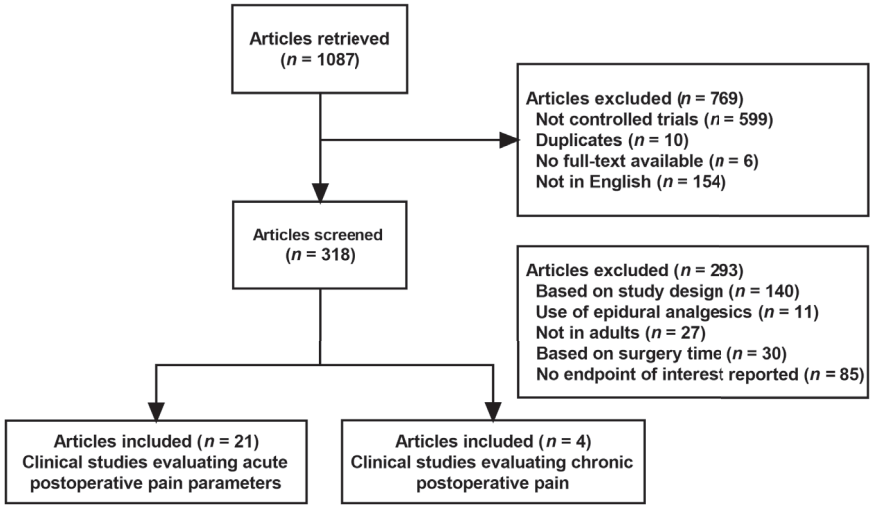

Figure 1. The Consort diagram

On February 6, 2015, the search strategy resulted in 1087 citations from 1993 until that date. Medline searches resulted in 474 articles, of which 431 studies were excluded. The Embase search resulted in 613 articles, which were all excluded. The search results and selection flow chart are reported in Figure 1. The review included 25 studies, 21 randomized studies evaluating the intraoperative use of remifentanil and reporting acute postoperative parameters and four studies evaluating the influence of intraoperative use of remifentanil on chronic postoperative pain.

Definitions

The terms "acute opioid tolerance" and "opioid induced hyperalgesia" originate from animal studies but were later on also used in human studies. Acute opioid tolerance is defined as "the need for a higher dose of the opioid to get the same analgesic effect"[11,26]. The underlying mechanism of acute opioid tolerance is thought to be desensitization of the opioid receptors[11]. Hyperalgesia is defined as "increased pain from a stimulus that normally provokes pain"[27]. It occurs at different locations surrounding the original pain site and has other characteristics than the original pain[11]. Although acute opioid tolerance and OIH have distinct mechanisms, either phenomenon may result in inadequate analgesia in patients treated with opioids[26]. Chronic postoperative pain is defined by the International Association for the Study of Pain (IASP) as pain that develops after surgical

intervention and lasts at least two months, while other causes of pain have been excluded[3,6]. Others have recommended to consider a period of three months rather than the two months suggested by the IASP[28].

Results

Studies evaluating intraoperative remifentanil and acute postoperative pain parameters

Table 1 shows the characteristics of the 21 retrieved clinical studies on acute postoperative pain. In 13 studies, remifentanil was administered together with volatile anaesthetics such as desflurane, isoflurane, sevoflurane, and nitrous oxide. Four studies investigated TIVA in combination with remifentanil. The remaining four studies combined or compared different anaesthetic techniques or compared with or without the combination with remifentanil (Table 1). Study arms or endpoints that were not of interest for this review are not displayed in Table 1. Eight of the 21 studies randomized between a low dose of remifentanil group (0.05 to 0.10 μg/kg/h) and a higher dose (0.15 to 1.0 μg/kg/h). The pain scales used in the different studies varied in score range (0 to 3, 0 to 5, 0 to 10) and methodology (visual, verbal of numerical). The VAS (range, 0 to 10 or 0 to 100 mm) and the (verbal) Numerical Rating Scale (range, 0 to 10) predominated. These scales have been validated for the measurement of acute pain[29].

Postoperative pain intensity

All 21 retrieved studies measured postoperative pain intensity (Table 2). Thirteen studies evaluated remifentanil during maintenance of anaesthesia with volatile agents. Six out of 13 studies randomized between different doses of intraoperative remifentanil (Table 2)[30–35]. A dose-dependent effect on pain scores was shown in 3 studies comparing a low remifentanil dose (0.05 μg/kg/min[30,31] or 0.1 μg/kg/min[32]) with a high dose (0.3 μg/kg/min). No other opioids, besides transition opioids, were used during surgery, and postoperative analgesia was facilitated through a "patient-controlled-analgesia" pump. In all 3 studies, the high dose was associated with higher pain scores. The effect of remifentanil on postoperative pain was prolonged, judged from the fact that patients in the high dose group still had higher pain scores after 3 to 4 hours[32], 12 hours[30,31] or 24 hours[31]. Even though the studies of Lee et al.[30,31] found a significant increase in pain intensity at different time points (Table 2), absolute values for pain intensity were low (i.e. at 24 hours VAS pain scores (mm) of 13.7 ± 4.9 vs. 23.8 ± 6.8 ($p<0.05$))[31]. In contrast to the reports described above, the 3 other studies that compared low-dose remifentanil with a higher dose of remifentanil did not reveal any effect on postoperative pain

intensity 1 hour[34] after surgery, during the first 6 hours after surgery[35], and 48 hours after surgery[33].

Of the 13 studies including volatile anaesthesia to evaluate remifentanil, 7 studies[36–42] compared remifentanil with different comparator arms. The study of Lison et al.[36], did also find a significant difference in pain intensity (0 to 4 pain scale) in the first hour after surgery between the remifentanil and sufentanil groups[36]. The authors of a desflurane-based study compared remifentanil with placebo[37]. Although desflurane has no analgesic features, no other opioids were used in the placebo group. Moreover, no long-acting opioid was used before the end of surgery. Still, pain intensity (100 mm VAS) in the remifentanil arm (0.3 μg/kg/min) was higher after 30 min, and after 6 and 12 hours. Remifentanil was also compared to magnesium sulphate during middle-ear surgery[38]. Pain scores were measured only 15 and 30 minutes after extubation and they were increased in the remifentanil group.

Four studies[39–42] evaluated remifentanil during maintenance of anaesthesia with volatile agents and nitrous oxide (Table 1). Two of these 4 studies found that despite the use of transition opioids before the end of surgery, the postoperative pain intensity for remifentanil was increased compared to sufentanil and adenosine[40,42]. The study of Minkowitz[39] compared fentanyl with remifentanil in combination with isoflurane and nitrous oxide and did not find any effects of remifentanil on postoperative pain intensity. The study of Lee and colleagues randomized between remifentanil (0.17 μg/kg/min) and nitrous oxide (70%) during isoflurane based anaesthesia, in which no significant differences in postoperative pain and postoperative morphine consumption were found[41].

Four studies used TIVA next to remifentanil as maintenance of anaesthesia in patients undergoing cardiac surgery[43–46]. All these studies did not report any increased postoperative pain induced by remifentanil. The study of Rauf et al.[43] randomized between remifentanil and placebo during propofol and fentanyl-based anaesthesia. The difference in pain intensity between groups did not reach significance (p=0.07), probably because the study was not powered on this endpoint[43]. A study on 90 patients comparing remifentanil with placebo during sufentanil and propofol-based anaesthesia found that pain scores at rest were comparable between the groups. However, pain scores during a deep breath were significantly lower in the remifentanil group directly after extubation, and at 8 and 16 hours post-surgery[44]. The study of Richebe et al.[45] compared different dosages after continuous infusion vs. target-controlled infusion of remifentanil.

Table 1. Basic characteristics of clinical studies in surgical patients (n = 21)

	Total (n)	Type of surgery	Anaesthetic Agents	Study arms of interest	n per arm	Maintenance dose remifentanil (μg/kg/min)
Maintenance of anaesthesia with volatile agents.						
Lee et al.[30]	90	Abdominal	DES	Remifentanil (low dose)	30	0.05
				Remifentanil (high dose)	29	0.3
Lee et al.[31]	85	Abdominal	DES	Remifentanil (low dose)	28	0.05
				Remifentanil (high dose)	29	0.3
Guignard et al.[32]	49	Abdominal	DES	Remifentanil (low dose)	25	0.1
				Remifentanil (high dose)	24	0.3
Joly et al.[33]	74	Abdominal	DES	Remifentanil (low dose)	25	0.05
				Remifentanil (high dose)	25	0.4
Song et al.[34]	75	Abdominal	DES	Remifentanil (low dose)	25	0.1
				Remifentanil (high dose)	25	0.3
Treskatch et al.[35]	48	Abdominal	SEV	Remifentanil (low dose)	15	0.08
				Remifentanil (high dose)	17	0.2
Lison et al.[36]	113	Cardiac	ISO	Remifentanil	57	1.0
				Sufentanil	56	0.02
Lee et al.[37]	75	Abdominal	DES	Remifentanil	25	0.3
				Saline	25	-
Ryu et al.[38]	80	Middle ear	SEV	Remifentanil	40	0.15
				Magnesiumsulphate	40	31.5 mg/kg/min
Minkowitz et al.[39]	210	Major*	ISO, N_2O	Remifentanil	139	0.5
				Fentanyl	71	1.0 μg/kg/hr
Fukunaga et al.[40]	62	Major*	DES, N_2O	Remifentanil	31	0.05-0.5
				Adenosine	31	50-500
Lee et al.[41]	60	Abdominal	ISO	Remifentanil	30	0.05
				N_2O	30	0.5

	Total (n)	Type of surgery	Anaesthetic Agents	Study arms of interest	n per arm	Maintenance dose remifentanil (µg/kg/min)
Derrode et al.[42]	30	Abdominal	DES, N_2O	Remifentanil	15	0.15
				Sufentanil	15	0.01
Maintenance of anaesthesia with TIVA						
Rauf et al.[43]	20	Cardiac	Prop, FENT	Remifentanil	10	0.1
				Saline	10	-
Lahtinen et al.[44]	90	Cardiac	Prop,SUF	Remifentanil	45	0.3
				Saline	45	-
Maddali et al.[46]	176	Cardiac	Prop	Remifentanil	59	1,00
				Fentanyl	58	0.025-0.15
Richebe et al.[45]	38	Cardiac	Prop	Remifentanil (low dose)	19	7 ng/ml*
				Remifentanil (high dose)	19	0.3
Maintenance of anaesthesia using a combination of volatile and intravenous agents						
Yeom et al.[47]	60	Spinal fusion	SEV, N_2O	Remifentanil	20	0.03
				Saline	20	-
			Prop	Remifentanil	20	0.16
Shin et al.[48]	186	Breast cancer	SEV	Remifentanil (low dose)	46	1 ng/ml†
				Remifentanil (high dose)	50	4 ng/ml†
			Prop	Remifentanil (low dose)	42	1 ng/ml†
				Remifentanil (high dose)	48	4 ng/ml†
Jo et al.[49]	60	Gyn-aecological	Prop, N_2O	Remifentanil	20	3-4 ng/ml†
				Saline	20	-
Gaszynski et al.[50]	57	Abdominal	Prop, N_2O	Remifentanil	20	0.25-1.5
				Fentanyl	15	0.025-0.15
				Alfentanil	22	1.0-1.5

* Surgery not specified. † target concentration with target-controlled infusion.
DES indicates desflurane; FEN, fentanyl; ISO, isoflurane; N_2O, nitrous oxide; Prop, propofol; SEV, sevoflurane; SUF, sufentanil; TIVA, total intravenous anaesthesia.

Table 2. Outcome of clinical studies in surgical patients (n = 21)

Study	End Points	Results
Maintenance of anaesthesia with volatile agents.		
Lee et al.[30]	Pain intensity after 1, 6, 12 and 24 h (100 mm VAS)	High dose remifentanil (HR) study arm had higher VAS scores at 1. 6 and 12 h after surgery compared to low dose (LR). (p<0.05)
	PCA (morphine/ketorolac/ ramosetron) use over 24 h (ml)	HR vs. LR: 60.0 ± 2.3 vs. 58.3 ± 2.6, p<0.05
	Time to first analgesic requirement (min)	HR vs. LR: 28.3 ± 8.3 vs. 37.5 ± 10.7, p<0.05
Lee et al.[31]	Pain intensity after 1, 6, 12 and 24 h (100 mm VAS)	Postoperative pain scores were significantly greater in the HR group at all time points compared to low dose (LR). (P<0.05)
	PCA (morphine/ketorolac/ ramosetron) use over 24 h (ml)	HR vs. LR: 51.4 ± 4.2 vs. 41.4 ± 6.2, p<0.05
	Time to first analgesic requirement (min)	HR vs. LR: 20.9 ± 8.6 vs. 30.2 ± 9.8, p<0.05
Guignard et al.[32]	Pain intensity until 24 h after surgery (0-10 VRS, 0-10 VAS)	15, 30 en 45 min after extubation VRS for pain were greater in the HR group. VAS pain scores were higher 3 and 4 hr after extubation in the HR group.
	Total morphine consumption at 24 hr after surgery (mg)	HR vs. LR: 59(43 to 71) vs. 32 (19 to 59), p<0.01
	Time to requesting additional morphine.	The high-dose remifentanil group required morphine significantly earlier. (p<0.05)
Joly et al.[33]	Pain intensity during 48 h after surgery (100 mm VAS, VRS)	No statistically significant differences in pain among groups.
	Total morphine consumption over 48 h (mg)	HR vs. LR: 86 (59 to 109) vs. 68(50 to 91), p<0.05
	Time to first analgesic requirement (min)	HR vs. LR: 24 (20 to 33) vs. 35 (28 to 46), NS
Song et al.[34]	Pain intensity (0-10 VAS) 1 hr after surgery.	HR vs. LR: 60.1 ± 20.3 vs. 58.0 ± 12.2, NS
	Analgesic consumption (ketorolac) the first hour after surgery (mg)	HR vs. LR: 27.0 ± 6.1 vs. 25.8 ± 6.9, NS
	PCA (morphine) use over 24 h (ml)	HR vs. LR: 60.1 ± 2.3 vs. 58.5 ±2.9, NS
	Time to first analgesic requirement (min)	HR vs. LR: 32. 2 ± 10.3 vs. 36.2 ± 11.9, NS
Treskatch et al.[35]	Pain intensity 0-6 hr after surgery (0-3 BPS, 0-4 VRS, 0-10 NRS)	No significant difference in postoperative pain intensity between groups.
	Total morphine consumption 6 h after surgery(mg)	HR vs. LR: 28 ± 5 vs. 30 ± 4, NS
	Time to first analgesic requirement (min)	HR vs. LR: 17 (10 to 21) vs. 12 (7 to 27), NS

Study	End Points	Results
Lison et al.[36]	Pain intensity (0-4 Pain scale) during first 3 h after weaning	Postoperative pain scores during the first hour of weaning were higher in the remifentanil group. (0.38 ± 0.42 vs. 0.24 ± 0.40, p<0.05)
Lee et al.[37]	Pain intensity after 30 min, 6, 12, 24 and 36 h (100 mm VAS)	Postoperative pain intensity was higher at 30 min, 6 h and 12 h in the remifentanil group compared to saline group. (P<0.05)
	PCA (morphine/ketorolac/ ramosetron) use over 36 h (ml)	Remi vs. saline: 88.88 ± 1.66 vs. 87.72 ± 1.49, p<0.01
	Time to first analgesic requirement (min)	Remi vs. saline: 34.0 ± 8.7 vs. 61.4 ± 5.3, p<0.01
Ryu et al.[38]	Pain intensity (0-100 mm VAS) the first 30 min after extubation	Only 15 and 30 min after extubation, higher pain scores were measured in the remifentanil group. (15 min: 53.5 (23.6) vs. 41.7 (19.2), p<0.05, 30 min: 53.5 (24.2) vs. 34.3 (17.8), p<0.05)
	The use of rescue analgesics (%)	Remi vs. Magnesium: 58% vs. 33%, P<0.05
Minkowitz et al.[39]	Pain intensity during 48 h after surgery (0-3 pain scale)	Groups were similar with respect to pain severity ratings at all postoperative times (until 48 h).
	Total morphine consumption 24 and 48 h after surgery	Total morphine consumption was not significantly different in both groups.
Fukunaga et al.[40]	Pain intensity after cough and deep breath until 48 h after surgery (0-10 VRNS)	Pain intensity 15 min after surgery in the remifentanil group was increased (9.0 ± 1.7 vs. 3.6 ± 3.3, p<0.001), this continued over the following 48 h. (p<0.01)
	Total morphine consumption over 48 h (mg)	Total morphine consumption was increased in the remifentanil group after 15 min (NS), 2 h (24 ± 8 vs. 7 ± 6, p<0.001) and 48 h (92 ± 35 vs. 53 ± 26, p<0.001)
Lee et al.[41]	Pain intensity at rest and movement 24 h after surgery. (0-10 VAS)	There was no difference pain scores during 24 h after surgery. (NS)
	Total morphine consumption the first 24 h	No significant differences between groups.
Derrode et al.[42]	Pain intensity until 12 h after surgery (0-10 VAS)	The remifentanil group had higher VAS scores the first 2 h after extubation.
	Total morphine consumption at 24 h after surgery (mg)	Remi vs. Sufentanil: 56 (29) vs. 37 (20), p<0.05
	Time to first analgesic requirement (min)	Remi vs. Sufentanil: 11 (1-29) vs. 55 (2-240), p<0.001
Maintenance of anaesthesia with TIVA		
Rauf et al.[43]	Pain intensity during the first hour after surgery (0-10 VAS)	Remi vs. Saline: 5 (2–9) vs. 3 (0–6), NS
	Morphine consumption during the first hour after surgery (mg)	Remi vs. Saline: 8.2 vs. 3.3, p<0.05
	Total morphine consumption 12 h after surgery (mg)	Remi vs. Saline: 27.1 (8.7) vs. 24 (6.6), NS

Study	End Points	Results
Lahtinen et al.[44]	Pain intensity at rest and after cough during 40 h (100 mm VAS)	The remifentanil group showed lower pain scores during deep breath immediately after extubation and 8 and 16 h after extubation. (P=0.02)
	Time to first analgesic requirement (min)	Remi vs. Saline: 9 (0-525) vs. 8.8 (0-170) . NS
	Total oxycodon consumption 48 h after surgery (mg)	Remi vs. Saline: 98 (29-166) vs. 99 (42-219). NS
Maddali et al.[46]	Pain intensity during 12 h (100 mm VAS)	No significant differences in pain intensity the first 12 h after surgery.
	The use of rescue analgesia (%)	Remi vs. fentanyl: 76.1% vs. 76.2%, NS
Richebe et al.[45]	Pain intensity at rest and movement during 44 h. (0-10 VAS and VRS)	No significance difference in VRS and VAS at rest and cough at different time points.
	Total morphine consumption after 48 h (mg)	HR vs. LR: 33 (31) vs. 31 (17), NS
Maintenance of anaesthesia using a combination of volatile and intravenous agents		
Yeom et al.[47]	Pain intensity at rest during 48 h (0-10 NRS)	Pain intensity did not differ significantly between groups the first 48 h postoperatively
	Total fentanyl consumption 48 h after surgery (μg)	No significant difference were found in PCA fentanyl requirements 48 h after surgery.
Shin et al.[48]	Pain intensity (0-10 VAS) during 24 h	The VAS scores during 24 h after surgery were higher in the high remifentanil-sevoflurane group than the other 3 groups. ($p<0.001$)
	Total morphine consumption after 24 h (mg)	Morphine consumption was higher in the high remifentanil - sevoflurane group vs. other groups. (38.6 ± 14.9 vs. 31.5 ± 3.7 vs. 31.7 ± 8.3 vs. 30.1 ± 6.1, $p<0.001$)
Jo et al.[49]	Pain intensity at rest and after cough and fentanyl use over 48 h (100 mm VAS)	Only 2 h after surgery pain intensity was lower in patients at rest in the remifentanil group. (36.5 ± 14.6 vs. 26.5 ± 9.3, $p=0.002$)
	Total fentanyl consumption 24 h after surgery (μg)	Remi vs. Saline: 756.5 ± 502.4 vs. 651.6 ± 367.5, NS
	Fentanyl titration dose (μg)	Remi vs. Saline: 227.5 ± 88.1 vs. 133.8 ± 87.8 , $p=0.001$
Gaszynski et al.[50]	Pain intensity during 6 h (0-5 verbal scale)	Significantly more patients in the remifentanil group reported disturbing pain. (25% vs. 13.3% vs. 4.5%, $p<0.05$)
	Analgesic consumption the first 6 h postoperatively	More analgesics were used in the remifentanil group. ($p<0.05$)

NRS indicates Numerical Rating Scale; NS, not significant; PCA, patient-controlled analgesia; VAS, Visual Analogue Scale; VRS, Verbal Rating scale

No difference was found in postoperative pain scores. Lastly, the study of Maddalli et al.[46] randomized between high dose remifentanil (1.0 μg/kg/min) and fentanyl (0.025 to 0.15 μg/kg/min) during cardiac surgery. After surgery, the fentanyl group continued with a reduced dose of fentanyl, whereas the remifentanil group received a bolus of fentanyl (1.0 μg/kg) at the end of surgery. No differences in pain intensity were measured during the first 12 hour after surgery.

Finally, four studies evaluated remifentanil using different anaesthetic regimens, or combined TIVA with volatile anaesthetics (Table 1)[47–50]. The study of Yeom et al.[47] compared three regimens: sevoflurane/nitrous oxide, sevoflurane/remifentanil/nitrous oxide, and propofol/remifentanil. No significant differences were seen in postoperative pain intensity after surgery. It is noteworthy that the remifentanil dosage was low in both groups (resp. 0.03 μg/kg/min and 0.16 μg/kg/min) compared to previously discussed studies[30–32]. Shin et al.[48], compared similarly low dosages of remifentanil (0.06 versus 0.15 μg/kg/min) when combined with sevoflurane or propofol (Table 1). Highest pain scores 24 hours after surgery were found in the highest remifentanil dose in the sevoflurane group[48]. The study of Jo et al.[49] combined propofol with nitrous oxide and randomized between remifentanil and placebo. This study found lower pain scores at rest in de remifentanil group. The placebo group received analgesics during postoperative phase only. Yet another study that maintained anaesthesia with propofol and nitrous oxide, found more disturbing pain, but less "small pain" in the remifentanil group versus the fentanyl and alfentanil groups[50].

Analgesic consumption

Of the 21 retrieved studies, 20 studies measured postoperative analgesic consumption, use of rescue analgesics, and/or time to first analgesic requirement. The most common endpoint with respect to postoperative analgesic consumption was total analgesic consumption over 24 hours.

Four out of 6 studies with volatile anaesthetics evaluated different doses of remifentanil and reported a significantly higher volume used of the patient-controlled analgesia pump over the first 24 postoperative hours in the (high dose) remifentanil group, even though relative differences were small[30–32,37]. When remifentanil was compared to another drug, that is, adenosine, magnesium sulfate, or sufentanil, the administration of remifentanil was also associated with increased requirements of postoperative analgesics (Table 2)[38,40,42]. In four studies with volatile anaesthetics, no significant difference was found between groups in total analgesic consumption[34,35,39,41].

When time to first analgesic requirement was used as an endpoint, results were also inconclusive. Five studies found a significant difference between the study arms, in which the time of the first analgesic requirement varies from 9 to 55 minutes in the (high dose) remifentanil group compared to the low-dose remifentanil group or comparative group[30–32,37,42]. Three other studies did not find any effect of remifentanil on time to first analgesic requirement[33–35].

One of four TIVA studies reported a significantly higher morphine consumption during the first hour after surgery in the remifentanil group[43]. The difference was, however, no longer significant at 12 hours. Patients in both groups received a 15 μg/kg bolus of fentanyl at induction of anaesthesia and additional boluses of fentanyl during surgery. The total fentanyl consumption in both groups was not reported. Although a statistical difference between postoperative analgesic consumption was found, the absolute morphine consumption was low (8.2 vs. 3.3 mg, $p<0.05$)**.** The other 3 studies that used TIVA reported no increase in total postoperative analgesic use in the remifentanil-treated patients[44–46]. To maintain anaesthesia two of these studies used long-acting opioids (e.g., sufentanil and fentanyl) next to propofol[43,44].

Concerning studies in which remifentanil was combined with a combination of volatile and intravenous agents, the study of Shin et al.[48] found higher morphine consumption after 24 hours in the high-dose remifentanil-sevoflurane group compared to the low-dose remifentanil-sevoflurane group or the remifentanil-propofol group. Two studies combining remifentanil with propofol/nitrous oxide found a higher titration dose[49] and a higher analgesic consumption 6 hours after surgery[50] in the remifentanil group. No differences in analgesic consumption were found between groups in the study of Yeom et al.[47]

OIH or acute opioid tolerance measured with Quantative Sensory Testing (QST)

In total, 5 of the 21 retrieved studies aimed for an objective quantification of sensation using QST, thereby exposing patients to pressure, thermal, and electrical stimuli. Four studies were performed with volatile anaesthetics[30,31,33,34] and one with intravenous agents[45]. None of these studies had acute opioid tolerance as endpoint. All 5 studies found a significantly enlarged area of hyperalgesia or significant decreased sensory threshold in patients receiving (high dose) remifentanil.

Joly et al.[33] studied two dosages of remifentanil (0.05 vs. 0.40 μg/kg/min) and did not find a difference in pain levels using the VAS between the two groups. However, measuring the area of hyperalgesia with QST, they found that the

area of hyperalgesia near the incision was significantly enlarged, and tactile pain thresholds adjacent to the incision were significantly decreased both at 24 and 48 hours after surgery in the high-dose remifentanil group. In contrast, tactile and pressure pain thresholds measured on the forearm did not differ between groups or between the time points before and after surgery.

In the studies of Song et al.[34] and Richebe et al.[45], the authors compared two different dosages of remifentanil. No dose-dependent effect of remifentanil was found on pain levels or analgesic requirements. Again, measured with QST, the tactile pain threshold was increased and the area of hyperalgesia near the incision, was significantly increased up to four days after surgery[34,45].

Moreover, two studies collected, in addition to standard postoperative parameters, hyperalgesia thresholds near the incision before and 24 hours after surgery. Both studies reported a significantly lower hyperalgesia threshold 24 hours after surgery in the high-dose (0.3 μg/kg/min) remifentanil group, indicating prolonged sensory changes after exposure to high-dose remifentanil[30,31].

Studies evaluating intraoperative remifentanil and long-term effects on pain parameters

Four studies addressed chronic postoperative pain and its possible association with the intraoperative use of remifentanil. Although all studies evaluated long-term effects of remifentanil on pain parameters, they varied in type of surgery, the sample size, and the study design as shown in Table 3.

The study of Salangros[51] compared low-dose remifentanil plus preoperative epidural analgesics with high-dose remifentanil plus postsurgical epidural analgesics after cardiac surgery. The incidence of chronic thoracic pain was significant higher in the high-dose remifentanil group after three months (50% vs. 16.7%), 6 months (55% vs. 16.7%), and at the end of the study (55% vs. 11.1%; median follow-up 9.5 months). However, the timing of the epidural block was different in both groups, which may have influenced the outcome[52].

The follow-up study in 90 cardiac patients compared the prevalence of chronic thoracic pain after 12 months upon the intraoperative use of remifentanil combined with fentanyl versus fentanyl alone[53]. Remifentanil was a risk factor for the development of chronic pain at 12 months (odds ratio 8.9, 95% confidence interval: 1.6 to 49.0) and a higher dose of remifentanil was more correlated with chronic pain than a lower dose. A point of concern is that remifentanil was given concomitantly with fentanyl, but despite this, a dose dependent relation was found.

Table 3: Clinical studies in surgical patients with effects of remifentanil on chronic postoperative pain (n = 4)

Study	Total (n)	Type of surgery	Study design	Outcome
Salengros et al.[51]	38	Thoracotomy*	RCT	High dose remifentanil without epidural analgesia had high incidence of CPP compered to low-dose with epidural analgesia.
Van Gulik et al.[53]	90	Cardiac	Prospective follow-up	Use of remifentanil was associated in a dose related manner with CPP.
Song et al.[54]	366	Lung and oesophageal cancer	RCT	Increased incidence of CPP in remifentanil-sevoflurane group vs the remifentanil-propofol group.
Cho et al.[55]	175	Breast cancer	Retrospective cohort	Increased incidence of CPP in remifentanil-sevoflurane group vs the remifentanil-propofol group.

* Type of surgery not specified.

CPP indicates chronic postoperative pain; RCT, randomized controlled trial.

In a prospective study, intrathecal analgesics were combined with sevoflurane (volatile group) or propofol and remifentanil (TIVA group)[54]. Acute pain intensity after surgery did not differ between both groups. However, chronic thoracic pain was significantly lower in the TIVA group after three months (38% vs. 57%, p=0.001) and 6 months (34% vs. 51%, p=0.002) compared with the sevoflurane group. Still, determining the precise effect of remifentanil is problematic, because the total dose of remifentanil was not reported and patients received epidural analgesia during and after surgery in both arms.

Cho et al.[55] analysed in a retrospective study the influence of sevoflurane or propofol on remifentanil-based anaesthesia during breast surgery. Both groups received an equal amount of remifentanil during surgery, but the combination of remifentanil with a volatile agent was associated with a higher incidence of chronic postoperative pain. The combination of sevoflurane and remifentanil was significantly associated with a 1.5 times greater prevalence of chronic pain compared with the propofol and remifentanil combination.

Discussion

This review provides an update of the literature on intraoperative remifentanil in relation to postoperative pain intensity, analgesic consumption, OIH or acute opioid tolerance, and chronic postoperative pain. Although other recent reviews focus on opiates and acute postoperative pain[13,16], this review focuses

on administered coanaesthetics and evaluates the association between remifentanil and chronic postoperative pain. Overall, there are indications that intraoperative remifentanil used in combination with coanaesthetics may cause acute postoperative hyperalgesia, however, no firm conclusions could be made regarding postoperative acute pain intensity, opioid consumptions and chronic pain.

Several studies investigated the influence of remifentanil on pain parameters in a (placebo) controlled study design, without the use of other opioids and administered together with inhalational anaesthetics[30,31,37,40]. Studies with this design showed increased postoperative pain levels and analgesic consumption. In contrast, in all four TIVA studies, the administration of remifentanil did not attenuate the postoperative pain intensity. With focus on different anaesthetics techniques, the study of Shin et al.[48] is of special interest. This study compared remifentanil administered with different strategies for maintenance of anaesthesia (i.e. propofol vs. sevoflurane) and also found an increase in postoperative pain during 24 hours after surgery in the high-dose remifentanil-sevoflurane group, but not in the low-dose remifentanil-sevoflurane and remifentanil-propofol groups[48]. However, this effect was not replicated in another study with the same groups, except that nitrous oxide was added to the maintenance anaesthesia with sevoflurane[47].

A possible explanation for the findings described above may be that propofol and nitrous oxide antagonize the NMDA receptors, which results in less central sensitization, thereby attenuating the development of hyperalgesia or tolerance to opioids[18,19]. This is in line with the finding that the glutamergic system is instrumental in both opioid tolerance and OIH[56]. Volatile anaesthetics such as desflurane, sevoflurane, and isoflurane have poor analgesic properties and have a minor impact on NMDA receptors relative to the impact of nitrous oxide[57]. More specifically, a study comparing remifentanil-propofol-based anaesthesia with and without the addition of nitrous oxide found that the addition of nitrous oxide did not influence postoperative pain and cumulative morphine consumption but did reduce remifentanil induced hyperalgesia[58]. It cannot be excluded, however, that these results on the influence of coanaesthetics are explained by other unidentified variables. Most of the studies that used volatile anaesthetics concerned abdominal surgery, whereas TIVA studies concerned cardiac surgery. Postoperatively, cardiac surgery patients are sedated longer compared with abdominal surgery patients. As such, on recovery from anaesthesia, the effect of remifentanil may have worn off during sedation, which may potentially explain the absence of increased pain scores in the remifentanil groups when combined

with TIVA for cardiac surgery. It is unknown whether sensitization occurs during sedation and whether pain perception on the long term is affected. In contrast, remifentanil stands out among other opioids for its pharmacological effects and possible side effects, either directly or indirectly, on the NMDA receptor[59,60].

Another possible cause for acute postoperative pain induced by remifentanil may be the extremely short half-life of remifentanil. Upon cessation of remifentanil infusion and in the absence of transition analgesics, postoperative parameters such as pain scores and analgesic consumption may be prone to increase[30,31,37,40]. This hypothesis is, however, disputed by the results of studies in which patients receiving long-acting opioids before the end of surgery still reported an effect of remifentanil on postoperative pain or analgesic requirements[32,40]. Finally, results of studies using QST suggested that remifentanil may cause hyperalgesia. However, although areas of hyperalgesia were increased, there was not always an increase in pain scores, indicating that these findings may not be clinically relevant. It seems that pain scales are not always sensitive enough to measure the existence of hyperalgesia or are incapable of measuring hyperalgesia when no actual painful stimulus is given. As such, the clinical relevance of increased postoperative hyperalgesia measured with QST as a cause of acute postoperative pain or increased analgesic consumption is therefore still not known[61]. Even though there seems some evidence that remifentanil leads to higher acute postoperative pain levels, postoperative analgesic requirements, or both, study designs are divers and sample sizes small. Evidence regarding the association of intraoperative remifentanil and acute postoperative pain levels and analgesic requirements are conflicting. The frequency of pain measurements varied from a single measurement after awaking from anaesthesia to hourly or 12-hourly measurements. Postoperative pain management protocols varied considerably, depending on type of surgery, hospital, and country from which the study originates. Postoperative pain levels and/or analgesic consumption were not always the primary endpoint of the studies. A large number of retrieved articles were excluded because remifentanil was administered in both study arms and in the same dose. The number of excluded articles of language other than English is also a form of bias. Moreover, postoperative pain and the postoperative use of analgesics were often not measured. Nonetheless, a broad overview of articles is given that specifically focus on the intraoperative use of remifentanil. In addition, the exclusion criteria used narrowed the scope of this review to adults undergoing prolonged surgery. In our opinion, this group of patients is the most relevant since remifentanil is used extensively during general anesthesia[62,63]. The focus on prolonged surgery is chosen due to the implied that patients received higher

amounts of remifentanil and underwent more invasive and painful surgeries. Therefore, our conclusions cannot be extended to less invasive surgeries, with a lower total dose of remifentanil, even though studies are available that have found higher postoperative pain levels and analgesic requirements upon short procedures[64–66].

Future studies with the goal to investigate the synergic or confounding effect of volatile or intravenous anaesthetics along with the simultaneous infusion of remifentanil and the effect on management of postoperative pain and analgesic consumption are needed. Ideally, the follow-up time is minimally 3 months to be able to determine the long-term clinical relevance of potential acute tolerance or OIH. In general, it would be worthwhile to identify the influence of the intraoperative use of opioids on chronic postoperative pain, as was initiated recently for cardiac surgery[67]. The available studies addressing postoperative chronic pain are divers in study design, yet cautiously indicate that the use of remifentanil may have adverse consequences on the long term, for which it would be worthwhile to study the possible clinical relevance. Only a few chronic pain studies so far included outcomes such as opioid-related side effects, ability to mobilize, and psychical recovery, emotional functioning, and participant disposition. Standardized outcomes like these have been recommended to standardize research in the field of chronic postoperative pain[68,69].

In conclusion, although studies are divers and sample sizes small, there are indications intraoperative remifentanil used in combination with coanaesthetics may influence the occurrence of acute postoperative hyperalgesia and may result in chronic postoperative pain. The current research is inconclusive to make firm clinical recommendations, especially when volatile agents are used; still there seems to be some evidence of a physiological effect. To determine the clinical relevance of these findings, more research on the influence of coanaesthetics and remifentanil on acute pain and chronic postoperative pain are needed.

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Literature

1. Apfelbaum, J. L., Chen, C., Mehta, S. S. & Gan, and T. J. Postoperative Pain Experience: Results from a National Survey Suggest Postoperative Pain Continues to Be Undermanaged. *Anesth. Analg.* 97, 534–540 (2003).
2. Sommer, M. *et al.* The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur. J. Anaesthesiol.* 25, 267–74 (2008).
3. Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *Lancet* 367, 1618–1625 (2006).
4. van Gulik, L. *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur. J. Cardiothorac. Surg.* 40, 1309–1313 (2011).
5. Choinière, M. *et al.* Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. *CMAJ* 186, E213-23 (2014).
6. Macrae, W. A. Chronic post-surgical pain: 10 Years on. *Br. J. Anaesth.* 101, 77–86 (2008).
7. Mongardon, N. *et al.* Assessment of chronic pain after thoracotomy: a 1-year prevalence study. *Clin. J. Pain* 27, 677–81 (2011).
8. Goldstein, E., Farquhar, M., Crofton, C., Darby, C. & Garfinkel, S. Measuring hospital care from the patients' perspective: an overview of the CAHPS Hospital Survey development process. *Health Serv. Res.* 40, 1977–1995 (2005).
9. Angst, M. S. & Clark, J. D. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 104, 570–587 (2006).
10. Koppert, W. & Schmelz, M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Pract. Res. Anaesthesiol.* 21, 65–83 (2007).
11. Raffa, R. B. & Pergolizzi Jr, J. V. Opioid-induced hyperalgesia: is it clinically relevant for the treatment of pain patients? *Pain Manag. Nurs.* 14, e67-83 (2013).
12. Rivosecchi, R. M. *et al.* An evidence based systematic review of remifentanil associated opioid-induced hyperalgesia. *Expert Opin. Drug Saf.* 13, 587–603 (2014).
13. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
14. Westmoreland, C. L., Hoke, J. F., Sebel, P. S., Hug Jr, C. C. & Muir, K. T. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 79, 893–903 (1993).
15. Thompson, J. P. & Rowbotham, D. J. Remifentanil--an opioid for the 21st century. *Br. J. Anaesth.* 76, 341–343 (1996).
16. Kim, S. H., Stoicea, N., Soghomonyan, S. & Bergese, S. D. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front. Pharmacol.* 5, 108 (2014).
17. Guntz, E. *et al.* Effects of remifentanil on N-methyl-D-aspartate receptor: an electrophysiologic study in rat spinal cord. *Anesthesiology* 102, 1235–1241 (2005).
18. Jevtovic-Todorovic, V. *et al.* Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. *Nat. Med.* 4, 460–463 (1998).
19. Grasshoff, C. & Gillessen, T. Effects of propofol on N-methyl-D-aspartate receptor-mediated calcium increase in cultured rat cerebrocortical neurons. *Eur. J. Anaesthesiol.* 22, 467–470 (2005).

20. Martucci, K. T., Eisenach, J. C., Tong, C. & Coghill, R. C. Opioid-independent mechanisms supporting offset analgesia and temporal sharpening of nociceptive information. *Pain* 153, 1232–1243 (2012).
21. Chu, L. F. *et al.* Modulation of remifentanil-induced postinfusion hyperalgesia by the β-blocker propranolol in humans. *Pain* 153, 974–981 (2012).
22. Angst, M. S., Koppert, W., Pahl, I., Clark, D. J. & Schmelz, M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. *Pain* 106, 49–57 (2003).
23. Luginbühl, M. *et al.* Modulation of remifentanil-induced analgesia, hyperalgesia, and tolerance by small-dose ketamine in humans. *Anesth. Analg.* 96, 726–32, table of contents (2003).
24. Lenz, H. *et al.* Effects of COX inhibition on experimental pain and hyperalgesia during and after remifentanil infusion in humans. *Pain* 152, 1289–1297 (2011).
25. Chu, L. F., Dairmont, J., Zamora, A. K., Young, C. A. & Angst, M. S. The endogenous opioid system is not involved in modulation of opioid-induced hyperalgesia. *J. pain* 12, 108–15 (2011).
26. Chu, L. F., Angst, M. S. & Clark, D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin. J. Pain* 24, 479–496 (2008).
27. Pasero, C. & McCaffery, M. Opioid-induced hyperalgesia. *J. Perianesth. Nurs.* 27, 46–50 (2012).
28. Haroutiunian, S., Nikolajsen, L., Finnerup, N. B. & Jensen, T. S. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 154, 95–102 (2013).
29. Williamson, A. & Hoggart, B. Pain: a review of three commonly used pain rating scales. *J. Clin. Nurs.* 14, 798–804 (2005).
30. Lee, C., Kim, Y.-D. & Kim, J.-N. Antihyperalgesic effects of dexmedetomidine on high-dose remifentanil-induced hyperalgesia. *Korean J. Anesthesiol.* 64, 301–7 (2013).
31. Lee, C., Lee, H.-W. & Kim, J.-N. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. *Korean J. Anesthesiol.* 64, 19–24 (2013).
32. Guignard, B. *et al.* Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 93, 409–17 (2000).
33. Joly, V. *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 103, 147–55 (2005).
34. Song, Y.-K. *et al.* Interaction between postoperative shivering and hyperalgesia caused by high-dose remifentanil. *Korean J. Anesthesiol.* 66, 44–51 (2014).
35. Treskatsch, S., Klambeck, M., Mousa, S. A., Kopf, A. & Schäfer, M. Influence of high-dose intraoperative remifentanil with or without amantadine on postoperative pain intensity and morphine consumption in major abdominal surgery patients: a randomised trial. *Eur. J. Anaesthesiol.* 31, 41–9 (2014).
36. Lison, S., Schill, M. & Conzen, P. Fast-track cardiac anesthesia: efficacy and safety of remifentanil versus sufentanil. *J. Cardiothorac. Vasc. Anesth.* 21, 35–40 (2007).
37. Lee, C., Song, Y.-K., Jeong, H.-M. & Park, S.-N. 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.* 61, 244–50 (2011).

38. Ryu, J.-H., Sohn, I.-S. & Do, S.-H. Controlled hypotension for middle ear surgery: a comparison between remifentanil and magnesium sulphate. *Br. J. Anaesth.* 103, 490–5 (2009).
39. Minkowitz, H. S. Postoperative pain management in patients undergoing major surgery after remifentanil vs. fentanyl anesthesia. Multicentre Investigator Group. *Can. J. Anaesth.* 47, 522–8 (2000).
40. Fukunaga, A. F., Alexander, G. E. & Stark, C. W. Characterization of the analgesic actions of adenosine: comparison of adenosine and remifentanil infusions in patients undergoing major surgical procedures. *Pain* 101, 129–38 (2003).
41. Lee, L. H. Y., Irwin, M. G. & Lui, S.-K. Intraoperative remifentanil infusion does not increase postoperative opioid consumption compared with 70% nitrous oxide. *Anesthesiology* 102, 398–402 (2005).
42. Derrode, N., Lebrun, F., Levron, J.-C., Chauvin, M. & Debaene, B. Influence of peroperative opioid on postoperative pain after major abdominal surgery: sufentanil TCI versus remifentanil TCI. A randomized, controlled study. *Br. J. Anaesth.* 91, 842–9 (2003).
43. Rauf, K., Vohra, A., Fernandez-Jimenez, P., O'Keeffe, N. & Forrest, M. Remifentanil infusion in association with fentanyl-propofol anaesthesia in patients undergoing cardiac surgery: effects on morphine requirement and postoperative analgesia. *Br. J. Anaesth.* 95, 611–5 (2005).
44. Lahtinen, P., Kokki, H. & Hynynen, M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 105, 794–800 (2006).
45. Richebé, P. *et al.* Target-controlled dosing of remifentanil during cardiac surgery reduces postoperative hyperalgesia. *J. Cardiothorac. Vasc. Anesth.* 25, 917–25 (2011).
46. Maddali, M. M., Kurian, E. & Fahr, J. Extubation time, hemodynamic stability, and postoperative pain control in patients undergoing coronary artery bypass surgery: an evaluation of fentanyl, remifentanil, and nonsteroidal antiinflammatory drugs with propofol for perioperative and postoperativ. *J. Clin. Anesth.* 18, 605–10 (2006).
47. Yeom, J. H., Kim, K. H., Chon, M.-S., Byun, J. & Cho, S. Y. Remifentanil used as adjuvant in general anesthesia for spinal fusion does not exhibit acute opioid tolerance. *Korean J. Anesthesiol.* 63, 103–7 (2012).
48. Shin, S.-W. *et al.* Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. *Br. J. Anaesth.* 105, 661–7 (2010).
49. Jo, H. R. *et al.* Remifentanil-induced pronociceptive effect and its prevention with pregabalin. *Korean J. Anesthesiol.* 60, 198–204 (2011).
50. Gaszynski, T. M., Strzelczyk, J. M. & Gaszynski, W. P. Post-anesthesia Recovery after Infusion of Propofol with Remifentanil or Alfentanil or Fentanyl in Morbidly Obese Patients. *Obes. Surg.* 14, 498–503 (2004).
51. Salengros, J.-C. *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.* 24, 608–16 (2010).
52. Bong, C. L., Samuel, M., Ng, J. M. & Ip-Yam, C. Effects of preemptive epidural analgesia on post-thoracotomy pain. *J. Cardiothorac. Vasc. Anesth.* 19, 786–793 (2005).

53. van Gulik, L. *et al.* Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br. J. Anaesth.* 109, 616–22 (2012).
54. Song, J. G. *et al.* Incidence of post-thoracotomy pain: a comparison between total intravenous anaesthesia and inhalation anaesthesia. *Eur. J. Cardiothorac. Surg.* 41, 1078–1082 (2012).
55. Cho, A. R. *et al.* The effects of anesthetics on chronic pain after breast cancer surgery. *Anesth. Analg.* 116, 685–693 (2013).
56. Wilder-Smith, O. H. & Arendt-Nielsen, L. Postoperative hyperalgesia: its clinical importance and relevance. *Anesthesiology* 104, 601–607 (2006).
57. Petrenko, A. B., Yamakura, T., Sakimura, K. & Baba, H. Defining the role of NMDA receptors in anesthesia: Are we there yet? *Eur. J. Pharmacol.* 723C, 29–37 (2013).
58. Echevarria, G. *et al.* Nitrous oxide (N(2)O) reduces postoperative opioid-induced hyperalgesia after remifentanil-propofol anaesthesia in humans. *Br. J. Anaesth.* 107, 959–965 (2011).
59. Yuan, Y. *et al.* Glycogen synthase kinase-3beta contributes to remifentanil-induced postoperative hyperalgesia via regulating N-methyl-D-aspartate receptor trafficking. *Anesth. Analg.* 116, 473–481 (2013).
60. Li, Y. *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* 8, e77790 (2013).
61. Werner, M. U. Vanguard research in opioid-induced hyperalgesia - but guard the basics. *Pain* 153, 943–944 (2012).
62. Komatsu, R. *et al.* Remifentanil for general anaesthesia: a systematic review. *Anaesthesia* 62, 1266–1280 (2007).
63. Uchida, K. *et al.* Impact of remifentanil introduction on practice patterns in general anesthesia. *J. Anesth.* 25, 864–871 (2011).
64. Ozkose, Z., Yalcin Cok, O., Tuncer, B., Tufekcioglu, S. & Yardim, S. Comparison of hemodynamics, recovery profile, and early postoperative pain control and costs of remifentanil versus alfentanil-based total intravenous anesthesia (TIVA). *J. Clin. Anesth.* 14, 161–168 (2002).
65. Alper, I., Erhan, E., Ugur, G. & Ozyar, B. Remifentanil versus alfentanil in total intravenous anaesthesia for day case surgery. *Eur. J. Anaesthesiol.* 20, 61–64 (2003).
66. Mukherjee, K., Seavell, C., Rawlings, E. & Weiss, A. A comparison of total intravenous with balanced anaesthesia for middle ear surgery: effects on postoperative nausea and vomiting, pain, and conditions of surgery. *Anaesthesia* 58, 176–180 (2003).
67. de Hoogd, S. *et al.* Remifentanil versus fentanyl during cardiac surgery on the incidence of chronic thoracic pain (REFLECT): study protocol for a randomized controlled trial. *Trials* 15, 466 (2014).
68. VanDenKerkhof, E. G., Peters, M. L. & Bruce, J. Chronic pain after surgery: time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. *Clin. J. Pain* 29, 2–8 (2013).
69. Turk, D. C. *et al.* Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 106, 337–345 (2003).