

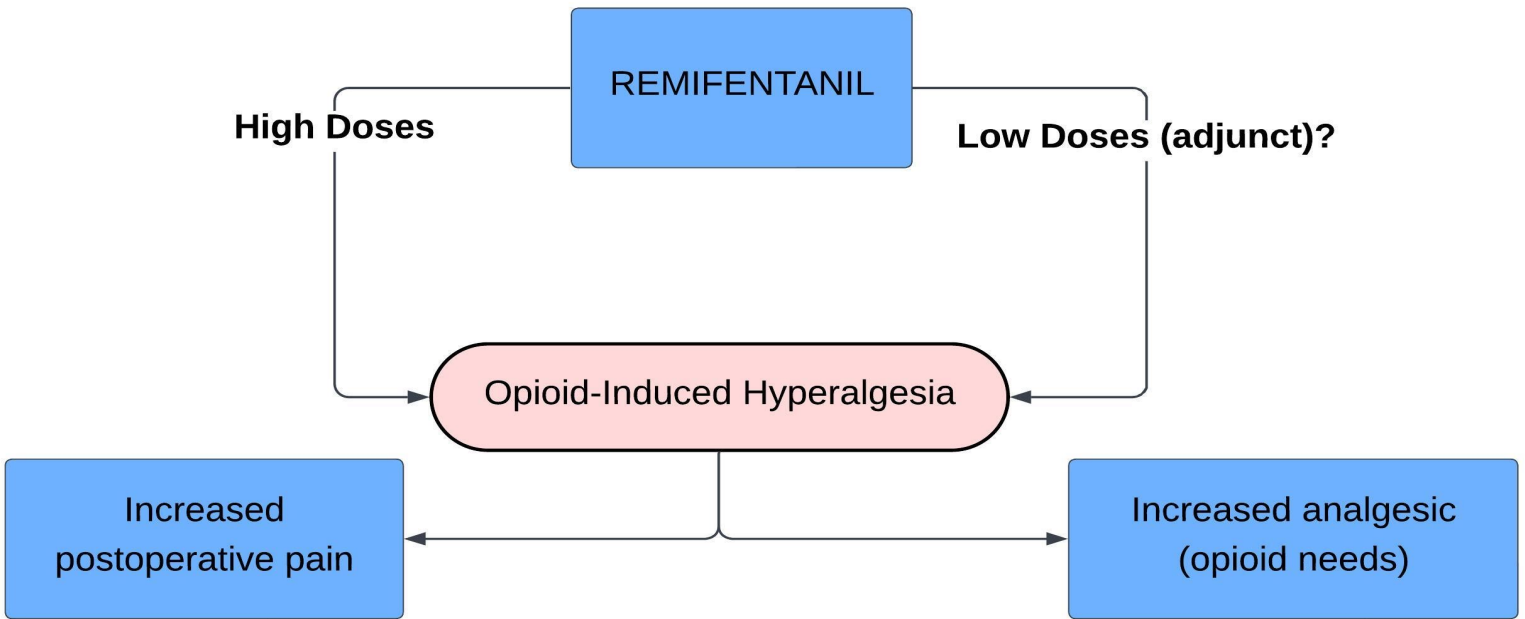
Low-dose remifentanyl as an adjunct is not associated with clinically important opioid-induced hyperalgesia

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INTRODUCTION



- High-dose remifentanyl is known to be associated with opioid-induced hyperalgesia (OIH).^{1,2}
- Low-dose remifentanyl is widely used and its potential for OIH has not been well-studied.
- We assessed outcomes of OIH with remifentanyl use as an adjunct analgesic after day surgeries.

METHODOLOGY

Design

- Prospective cohort study nested within a randomized trial showing no difference in achieving satisfactory analgesia with morphine or hydromorphone.

Patient Selection

- Patients having ambulatory surgeries (>1h) under general anesthesia (GA).
- Use of neuraxial or regional analgesia; use of long-acting opioids, ketamine or lidocaine were excluded.

Anesthesia management

- GA with multimodal analgesia including preop. dexamethasone and acetaminophen.
- Intraoperatively- fentanyl or sufentanyl were used with remifentanyl as an adjunct (anesthesiologist's discretion).
- No long-acting opioids

Analgesia management in PACU

- Equipotent doses of morphine or hydromorphone were administered by nurses to achieve minimal or no pain in post anesthesia care unit (PACU).³

Outcome measures

- Primary: worst pain scores in PACU and average pain scores during 24 h after surgery in patients.
- Secondary: pain scores and dose of rescue non-steroidal anti-inflammatory agents and long-acting opioids in PACU were collected.

Analysis

- Outcomes in remifentanyl group vs Non-remifentanyl group compared using Student's t test.
- The association of remifentanyl with our outcomes were explored using multivariate regression models, adjusting for patient and surgical variables.

RESULTS

- 276 of 402 patients (69%) had remifentanyl administration intraoperatively, along with other short-acting opioids.
- Baseline characteristics were comparable between the remifentanyl group (n=276) and non-remifentanyl opioid group (n=126) (**Table 1**).
- No differences in worst PACU pain scores or average pain scores 24 h after surgery: mean difference (MD) (95% confidence interval [CI]) 0.3 (-0.9, 0.2), and 0.4 (-1.7, 0.9), respectively (**Table 2** and **Figure 1**).
- In the remifentanyl group, the dose of long-acting opioids in PACU was statistically higher, but not clinically significant: MD, (95% CI) 0.97 mg morphine units (0.2, 1.7) p=0.01 (**Table 2**).
- Adjusted analyses indicated that higher doses of remifentanyl (25 mcg increments) were associated with:
 - higher worst pain scores in day surgery unit (before discharge): 0.23 units, (95% CI 0.05, 0.41), p=0.01;
 - higher average pain scores 24 h after surgery: 0.25 units, (95% CI 0.036, 0.46), p=0.02; and
 - higher long-acting opioid doses in PACU: 0.14 mg morphine units, (95% CI 0.02, 0.25), p=0.02 (**Table 3**).

Table 1: Baseline characteristics of study patients

Variable	Remifentanyl N= 276	No Remifentanyl N= 126	p-value [‡]
Age in years; mean (SD)	46.8 (14.4)	46.1 (12.8)	0.60
Female; n (%)	173 (63)	85 (67)	0.35
BMI; mean (SD)	27.5 (4.1)	26.8 (4.3)	0.14
Apfel score; mean (SD)	2.6 (1)	2.5 (0.9)	0.83
Depression score; median (IQR)	2 (1, 4)	2 (1, 4)	0.99
Anxiety score; median (IQR)	6 (3, 9)	6 (4, 9)	0.21
Catastrophizing score; median (IQR)	9 (2, 16)	10 (5, 19)	0.11
Preoperative pain in the operative area; n (%)	106 (38)	60 (48)	0.08
Chronic pain in other areas; n (%)	52 (19)	16 (13)	0.13

BMI: body mass index; n: number; SD: standard deviation; IQR: interquartile range with 1st and 3rd quartiles noted; [‡] p-value by Student's t-test for continuous variables and Chi-square test for binary variables.

Table 2: Exposure to low dose remifentanyl and postoperative outcomes of pain intensity, analgesic use and side effects

Outcome	Treatment group		OR (95% CI)	P-value
	Remifentanyl n=276	No Remifentanyl n=126		
Maximum pain scores during PACU stay; mean (SD)	5.6 (2.53)	5.3 (2.61)	0.3 (-0.9, 0.2)	0.24
Average pain scores in the first 24 h after surgery; mean (SD)	4.6 (2.28)	4.2 (6.61)	0.4 (-1.7, 0.9)	0.55
Secondary Outcomes				
Maximum pain scores in DSU	3.7 (6.07)	3.2 (1.95)	0.5 (-1.6, 0.6)	0.38
Dose of long-acting opioids in PACU	5.6 (3.77)	4.6 (3.19)	0.97 (0.2, 1.7)	0.01*
Need for NSAIDs in PACU; n (%)	124 (45)	45 (36)	3.2	0.07
Incidence of severe PONV; n (%)	12 (4.3)	2 (1.6)	1.96	0.16
Incidence of severe itching; n (%)	0 (0)	1 (0.8)	2.2	0.14

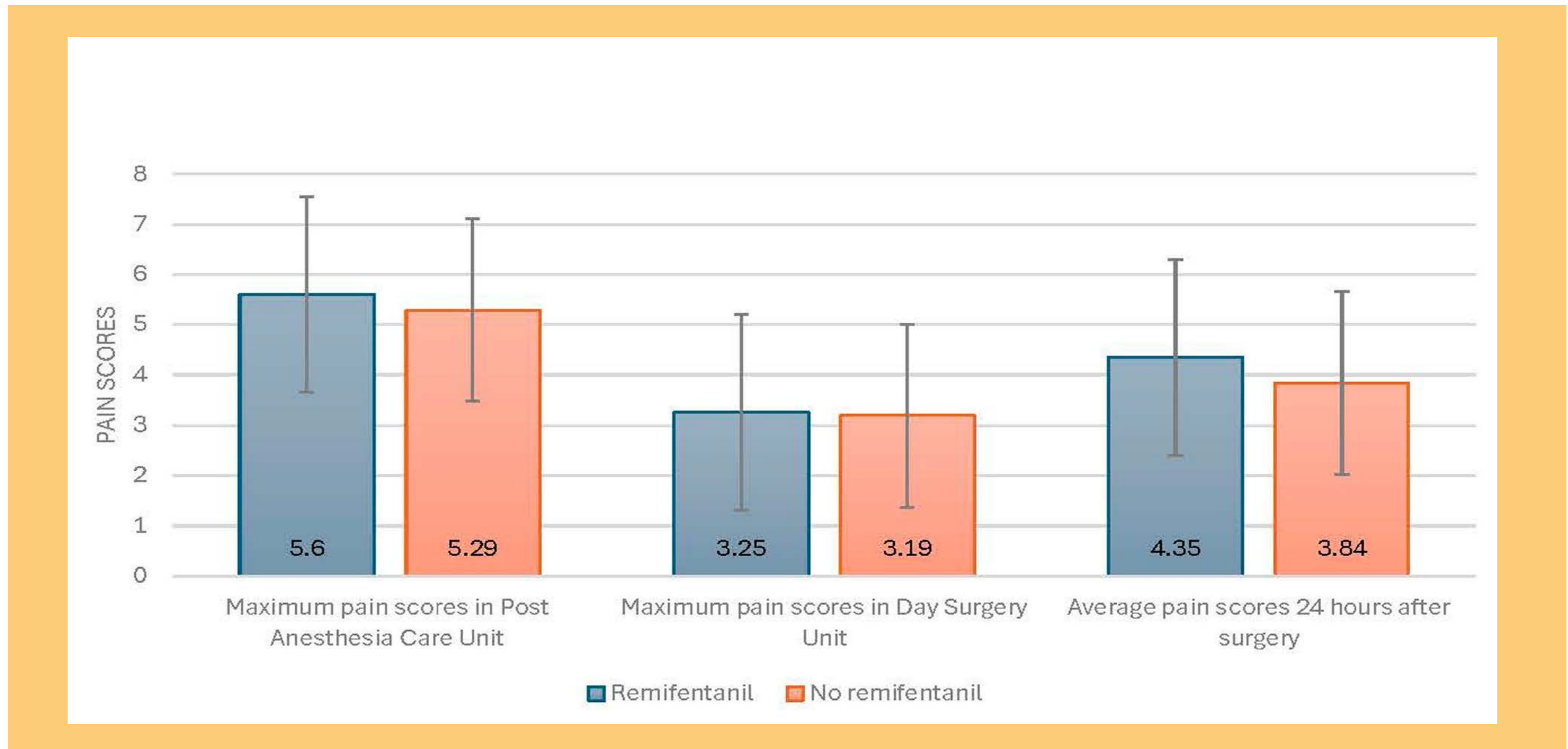
CI: confidence interval; DSU: day surgery unit; NSAID: nonsteroidal anti-inflammatory drug; PACU: post anesthesia care unit; PONV: postoperative nausea vomiting; SD: standard deviation
*statistically significant; *mean difference for continuous outcomes and chi-square for binary outcomes

Table 3: Association of remifentanyl administration and dose on pain scores and analgesic requirements

	Remifentanyl administration		Remifentanyl dose	
	Coefficient ^{\$§}	P-value	Coefficient ^{†*}	P-value
a) Maximum pain scores in PACU expressed in 0-10 scale				
Unadjusted	0.33 (-0.22, 0.87)	0.24	0.025 (-0.025, 0.1)	0.41
Adjusted	0.27 (-0.28,0.82)	0.33	0.07 (-0.013,0.16)	0.1
b) Maximum pain scores in DSU expressed in 0-10 scale				
Unadjusted	0.49 (-0.61, 1.58)	0.38	0.175 (0.02, 0.33)	0.03*
Adjusted	0.49 (-0.69, 1.67)	0.41	0.23 (0.05, 0.41)	0.01*
c) Average pain scores 24 hrs after surgery expressed in 0-10 scale				
Unadjusted	0.40 (-0.92, 1.72)	0.55	0.175(-0.02, 0.25)	0.08
Adjusted	0.57 (-0.85, 1.99)	0.43	0.25 (0.036, 0.46)	0.02*
d) Dose of long-acting opioids in PACU as mg of i.v. morphine equivalents (MME)				
Unadjusted	0.97 (0.20, 1.73)	0.01*	0.16 (0.05, 0.27)	0.005*
Adjusted	0.75 (-0.03,1.53)	0.06	0.14 [#] (0.02, 0.25)	0.02 [‡]
e) Need for rescue NSAIDs in PACU [@]				
Unadjusted	1.5 (0.96, 2.3)	0.07	1.05 (0.78, 1.104)	0.21
Adjusted	1.60 (0.98, 2.60)	0.06	1.01 (0.99, 1.004)	0.47

DSU: day surgery unit; NSAIDs: nonsteroidal anti-inflammatory drugs; PACU: post anaesthesia care unit; i.v: intravenous;
*statistically significant; ^{\$§}Coefficient equals mean difference in pain scores (table a-c) or dose of long-acting opioids in PACU (table d) between patients receiving remifentanyl and patients receiving other types of opioids.
+++Coefficient equals increase in pain score (table a-c) or dose of long-acting opioids in PACU (table d) for every 25mcg increase in remifentanyl dose. # PACU opioid use was more by 0.14 mg of i.v. morphine equivalent with 25mcg increase in remifentanyl; @ Coefficients represent odds ratio for the use of rescue NSAIDS
Covariates used in the adjusted model: age; sex; BMI; Apfel score; anxiety score; depression score; catastrophizing score; presence of preoperative pain in the surgical area; presence of chronic pain in other parts of the body; type of surgery (laparoscopic vs. open); surgical duration; total intraoperative opioid used in MME; and total dose of midazolam and propofol

Figure 1: Pain scores between patients who received or did not receive remifentanyl



DISCUSSION

- Low-dose remifentanyl, as an adjunct analgesic is not associated with OIH.⁴
- The increased opioid requirement of < 1mg morphine units in PACU with remifentanyl (opioid tolerance), is not clinically important.
- Clinicians can safely use remifentanyl in low doses, but the potential for OIH exists with higher doses.
- Clinicians should consider measures to decrease OIH, when remifentanyl is used for longer duration or higher doses.⁵

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The original RCT was funded by AbbVie New Investigator Award in Anesthesia, CAS-2014-038; Canadian Anesthesiologists' Society (2014); Department of Anesthesia, McMaster University. Canadian Institutes of Health Research RCT mentoring stipend grant award (between March 2017 and February 2018), Career Scientist Award, CAS-2018-062, Canadian Anesthesia Research Foundation (2018) (to HS).