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ORIGINAL RESEARCH ARTICLE

Intranasal Fentanyl for Intervention-Associated Breakthrough Pain After Cardiac Surgery

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Abstract

Background Cardiac bypass surgery patients have early postoperative interventions that elicit breakthrough pain. We evaluated the use of intranasal fentanyl for breakthrough pain management in these patients.

Methods Multimodal analgesia (paracetamol 1 g three times a day, oxycodone 2–3 mg boluses with a patient-controlled intravenous pump) was used in 16 patients (age 49–70 years, weight 59–129 kg) after cardiac bypass surgery. Intranasal fentanyl 100 µg or 200 µg was used to manage breakthrough pain on the first and third postoperative mornings in a randomised order. Blood samples were collected for up to 3 h after fentanyl administration, pain was assessed with a numeric rating scale of 0–10. Plasma fentanyl concentration was assayed using liquid chromatography-mass spectrometry. Body composition was measured with a bioelectrical impedance device.

Results Bioavailability of intranasal fentanyl was high (77%), absorption half-time short (< 2 min) and an analgesic plasma concentration ≥ 0.5 ng/mL was achieved in 31 of 32 administrations. Fentanyl exposure correlated inversely with skeletal muscle mass and total body water. Fentanyl analgesia was effective both on the first postoperative morning with chest pleural tube removal and during physiotherapy on the third postoperative morning. The median time of subsequent oxycodone administration was 1.1 h after intranasal fentanyl 100 µg and 2.1 h after intranasal fentanyl 200 µg, despite similar oxycodone concentrations (median 13.8, range 5.2–35 ng/mL) in both fentanyl dose groups.

Conclusions Intranasal fentanyl 100 µg provided rapid-onset analgesia within 10 min and is an appropriate starting dose for incidental breakthrough pain in the first 3 postoperative days after cardiac bypass surgery.

Clinical Trial Registration EudraCT Number: 2018-001280-22.

Key Points

Postoperative pain after cardiac bypass surgery is exacerbated by short-duration interventions such as chest drain removal or physiotherapy that can elicit breakthrough pain during recovery.

Intranasal fentanyl has high bioavailability (0.77) with a short absorption half-time (< 2 min).

Plasma concentrations ≥ 0.5 ng/mL were effective to control breakthrough pain after intranasal fentanyl 100 µg or fentanyl 200 µg given 10 min before known painful interventions.

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1 Introduction

Acute pain after cardiac surgery is often severe, and effective pain management is beneficial for recovery. Severe pain increases the risks for postoperative complications and decreases quality of life and function, and delays postoperative rehabilitation [1, 2]. In some patients, pain after surgery lasts beyond the natural healing of the tissues and may become chronic. Acute postoperative pain is one of the known modifiable predictors of persisting postoperative pain. The greater the magnitude of acute pain and the longer it lasts, the more likely are patients to have pain at 12 months after cardiac surgery [2–4]. Most patients need a multimodal approach to pain management in the early postoperative period. Opioids comprise a component of this multimodal approach [2].

Postoperative patients have both constant pain and sudden flares of breakthrough pain. Breakthrough pain is defined as an acute exacerbation of pain that is inadequately controlled by a stable analgesic regime. Breakthrough pain flares are both predictable and unpredictable. Short-acting opioid analgesics are often the primary treatment for this pain, and compounds that have a fast onset, a short duration of action and a convenient administration route are preferred [5]. Breakthrough pain episodes are often predictable in postoperative surgery patients. Predictable triggers for such pain in cardiac surgery patients are, for example, chest tube removal and postoperative physiotherapy; exacerbation of pain is anticipated, and a short duration of pain predicted.

Opioids differ in lipophilicity, opioid receptor binding affinity and intrinsic activity. These features contribute to differences in absorption, onset, potency and duration of action [6]. Fentanyl is a lipophilic opioid and it has been approved for intranasal transmucosal administration in patients with cancer with breakthrough pain. Intranasal fentanyl has a reported high bioavailability of 71%, maximum concentration in plasma is reached within 7 min of administration and the duration of action is approximately an hour [7]. Intranasal fentanyl has been used also in non-cancer acute pain [8, 9]. Intravenous (IV) opioid analgesics (e.g., oxycodone) are commonly used after cardiac surgery via a patient-controlled analgesia (PCA) pump as oral absorption of drugs is unpredictable during the first 48 h after surgery [10–13]. However, patient attachment to a PCA pump can limit mobility. Thus, transmucosal administration of fentanyl is an attractive non-invasive alternative for breakthrough pain in the early postoperative period [6, 8, 9, 14].

The aim of the study was to evaluate intranasal fentanyl for incidental breakthrough pain in patients after cardiac surgery. Our hypothesis was that chest pleural and mediastinal drainage tube removal and physiotherapy exacerbate pain in cardiac surgery patients and that while intranasal fentanyl 100 µg should be an effective analgesic to control these pain flares, a fentanyl 200-µg dose would provide a longer duration of analgesic action [7]. To test this hypothesis, we investigated exposure to fentanyl at two doses, 100 µg and 200 µg, and observed pain during the chest tube removal on the first postoperative morning and during physiotherapy on the third postoperative morning. Intranasal fentanyl absorption pharmacokinetic (PK) parameters were estimated because these characteristics contribute to the speed of onset of analgesia. Body composition was evaluated to assess this as a PK covariate that might have impact on fentanyl concentration.

2 Materials and Methods

2.1 Patients

Study patients were scheduled for elective cardiac bypass surgery with extracorporeal circulation in Kuopio University Hospital, Kuopio, Finland between February and June 2019. Patients were provided oral and written information about the trial protocol, and they all gave written consent. The study protocol was approved by the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland (Ref. 657//2018), the Finnish Medicines Agency was notified (Ref. 62//2018), and it was registered in the European Clinical Trials Database (Eudra CT: 2018-001280-22). The study was conducted in accordance with the Declaration of Helsinki and had institutional approval.

We enrolled patients aged between 18 and 75 years who had no known hypersensitivity to fentanyl or any ingredient in the intranasal pharmaceutical preparation. Patients were excluded if they had moderate or severe renal or hepatic impairment, sleep apnoea, respiratory depression with hypoxia and/or hypercapnia, chronic obstructive pulmonary disease or a history of opioid abuse. Patients who were treated with drugs known to inhibit or induce cytochrome P450 (CYP) 3A activity or inhibit CYP2D6 activity (e.g., CYP3A4; carbamazepine, imidazole derivatives and macrolide antibiotics; CYP2D6; paroxetine and quinidine) were excluded.

2.2 Anaesthetic Management and Extracorporeal Circulation

Patients arrived at the hospital on the day before the surgery. Each patient was interviewed and examined by a cardiac surgeon (AV) to determine eligibility for the study. Body composition was assessed using a bioelectrical impedance device (medical body composition analyser; seca mBCA

515; seca Deutschland, Hamburg, Germany) to determine height, weight, total body water, fat mass, visceral fat, fat-free mass and skeletal muscle mass.

Before surgery, the patients received oral premedication: diazepam 0.25 mg/kg up to 20 mg. Nitrides, beta-blockers, statins, cortisone and medication for chronic pulmonary disease were continued if these were existing routine medications. A standardised anaesthesia protocol was used for each patient. Anaesthesia was induced with IV midazolam (median 5 mg; range 3–5), sufentanil and propofol. Cisatracurium was used as a neuromuscular blocking drug. Anaesthesia was maintained with propofol infusion (1532 mg; 1216–2277), and sufentanil (200 µg; 100–250) and cisatracurium (26 mg; 20–38) boluses. Sevoflurane was added if the patient was hypertensive ($n = 7$, median 0.25 MAC hours, 0.1–1.29). A conventional extracorporeal circulation was used in all surgeries [11].

2.3 Postoperative Pain Management

All patients had a multimodal, postoperative pain management regime. Patients were given paracetamol 1 g three times a day; the first doses were IV and then by mouth starting on the first postoperative day. Rescue analgesia comprised IV oxycodone boluses; the first doses were given by the intensive care unit nurses and on the surgical ward patients used an IV PCA pump with oxycodone; single dose 2–3 mg, lock-out time 10 min, maximum dose 20 mg/4 h. Patients with insufficient pain relief, indicated by a 11-point numeric rating scale score ≥4/10 at rest or ≥6/10 during coughing or deep breathing, were allowed 6–8 mg of subcutaneous oxycodone by nursing staff. Following the study period, i.e., on the fourth postoperative day, the PCA pump was discontinued and patients were administered an oxycodone-naloxone tablet 10/5 mg by mouth twice a day together with paracetamol 1 g three times a day for the rest of their hospital stay. Cumulative oxycodone consumption for rescue analgesia via the IV PCA pump was recorded before intranasal fentanyl administrations on the first and third postoperative mornings, and during the first 3 h after the fentanyl administrations.

2.4 Intranasal Fentanyl Administration

The pharmaceutical preparation used in this study was Instanyl® (Takeda, Helsinki, Finland) in two strengths, 100 µg and 200 µg of fentanyl. Each patient was given a single dose of both strengths of medication in a blinded randomised sequence. In group 1, patients were administered the first dose of intranasal fentanyl; 100 µg, on the first postoperative morning 10 min before chest tube removal and the second dose, 200 µg, on the third postoperative morning just before physiotherapy, and in group 2, vice versa; 200 µg on the first postoperative morning and 100 µg on the third postoperative morning (see the flow chart in Fig. 1). Intranasal fentanyl was administered to each patient with the patient's head in an upright position during administration, the first dose in the intensive care unit on the first postoperative morning and the second dose at the surgical ward on the third postoperative morning by the same investigator (AV). The hospital pharmacy covered the nasal spray device labelling with an opaque tape and coded the devices to conceal the treatment allocation. Randomisation was generated with a random organisation generator (www.randomization.com).

2.5 Pain Intensity Assessment and Patient Monitoring

Pain intensity before and after chest tube removal on the first postoperative morning and before and during physiotherapy on the third postoperative morning was evaluated during the blood collection visits: (i) at rest, (ii) with coughing; and (iii) during a deep breath, using an 11-point numeric rating scale (0 = no pain, 10 = most pain). Arterial blood pressure, heart rate and rhythm, peripheral capillary oxygen saturation, respiratory rate, end-tidal carbon dioxide and adverse effects were recorded after each blood sample (see below). Adverse effects were sought also from patients' medical records.

2.6 Blood Samples

Blood samples (3 mL) for the drug assay were obtained from a central venous catheter before drug administration, and at 10, 20, 30, 40, 60, 120 and 180 min after fentanyl administration. Blood was collected into EDTA tubes, and plasma was obtained within 60 min of collection by centrifugation at 2100*g* for 10 min at + 20 °C. The separated plasma was stored at − 76 °C until analysis in a single batch.

2.7 Plasma Fentanyl and Oxycodone Concentrations

Fentanyl and oxycodone concentrations were analysed with a Waters Acquity ultra-performance liquid chromatograph combined with a Waters XEVO-TQ-S triple quadrupole mass spectrometry (Waters, Milford, MA, USA) in one single batch [15, 16]. The lower limits of quantification (LLoQ) were 0.004 ng/mL for fentanyl and 0.1 ng/mL for oxycodone. The linear calibration ranges were fitted as follows: fentanyl 0.004–40 ng/mL and oxycodone 0.1–200 ng/mL. Accuracies ranged for both analytes between 93 and 105% at the LLoQ and between 87% and 110% above the LLoQ. The precisions were 0.8–19% over the entire range of calibration. All fentanyl and oxycodone concentrations are reported as free base.

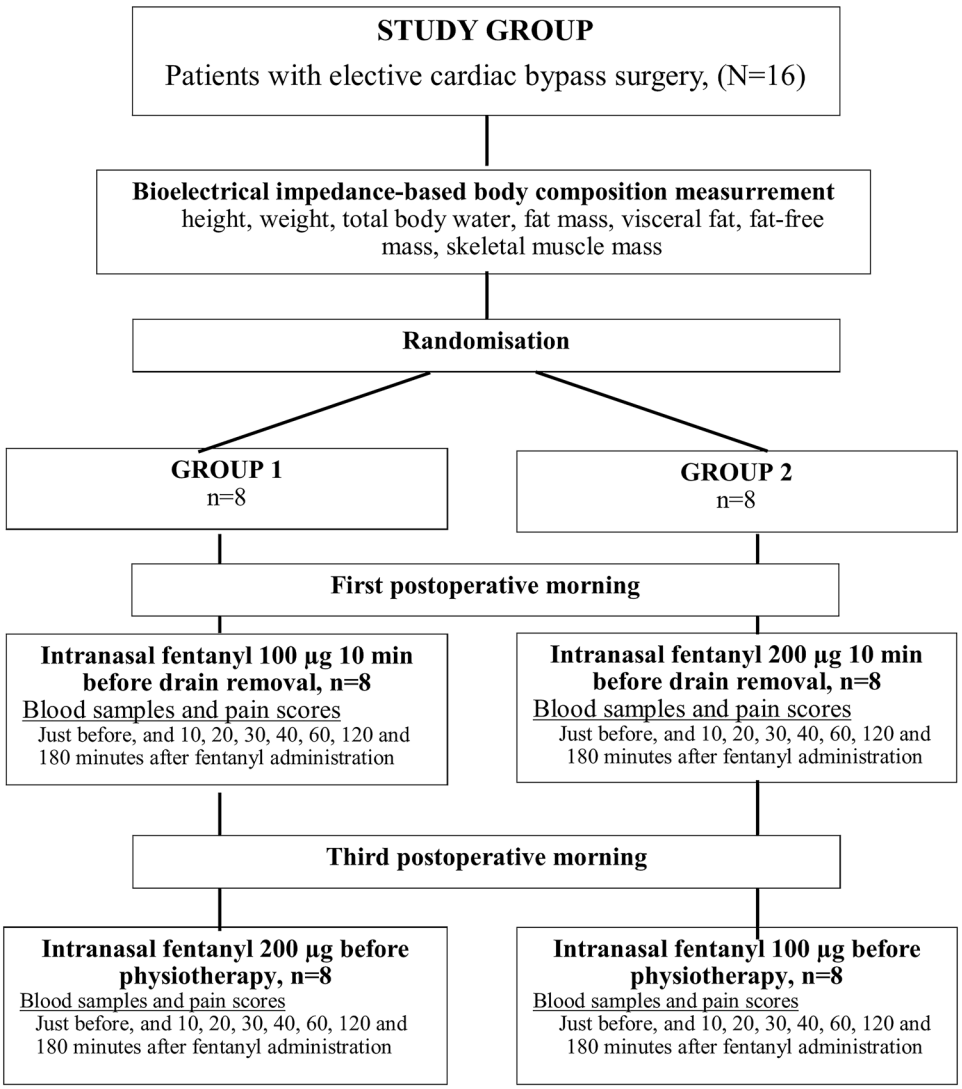

Fig. 1 Flow chart

2.8 Pharmacokinetic Modelling

Both non-compartmental and population PK modelling were used. The non-compartmental analysis was performed using Phoenix WinNonlin software version 6.3 (Certara, Princeton, NJ, USA). The maximum observed plasma drug concentration (C_{max}), time to C_{max} and area under the plasma concentration–time curve from time zero to the last quantifiable concentration ($AUC_{0–180}$) were determined. The $AUC_{0–180}$ was calculated using the linear trapezoidal rule. The figures for plasma concentration–time curves were created using the GraphPad Prism version 5 (GraphPad Software Inc., La Jolla, CA, USA). The time period with fentanyl concentration over 0.5 ng/mL was calculated with a non-compartmental analysis using linear interpolation rule (Phoenix WinNonlin 8.3, Princeton, NJ, USA).

Population parameter estimates were obtained using nonlinear mixed-effects models (NONMEM VII; Globomax LLC, Hanover, MD, USA). The population mean parameters, between-subject variance (BSV) and residual variance were estimated using the first-order conditional estimation method using ADVAN 12 TRANS 4 of NONMEM VII. Convergence criterion was 3 significant digits.

The population parameter variability was modelled in terms of random-effect (η) variables. Each of these variables is assumed to have a mean of 0 and a variance denoted by ω^2, which is estimated. Population parameter variability comes from two distinct sources; BSV and within-subject variation. If an individual is studied on more than one occasion, then the variability in the occasion-specific individual parameter around the average individual value defines within-subject variation. Within-subject variation should be divided into within-occasion variability and between-occasion variability (BOV) but within-occasion variability for a parameter such as clearance is difficult to estimate. In this study, intranasal fentanyl was given to individuals

on two occasions and BOV was estimated. Both BSV and BOV were modelled with an exponential term. We report the estimate of ω for each variability component expressed as a percentage because these quantities are approximate coefficients of variation for a log normal distribution. Residual unidentified variability was described using a combined proportional and an additive residual error model for each observation prediction (Err_{PROP}, Err_{ADD}).

2.8.1 Size Standardisation

The parameter values were estimated as standardised for a body weight of 70 kg using an allometric model [17].

$$P_i = P_{std} \times \left(W_i / W_{std} \right)^{PWR},$$

where P_i is the parameter in the ith individual, Wi is the weight in the ith individual and P_{std} is the parameter in an individual with a weight W_{std} of 70 kg. The PWR exponent was 0.75 for clearance and 1 for distribution volumes.

2.8.2 Quality of Fit

The quality of fit of the PK model to the data was sought by NONMEM's objective function and by visual examination of plots of observed vs predicted concentrations. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess significance, e.g., an objective function change of 3.84 is significant at $\alpha = 0.05$.

Bootstrap methods, incorporated within the Wings for NONMEM program, provided a means to evaluate parameter uncertainty [18]. A total of 1000 replications were used to estimate parameter confidence intervals. A visual predictive check [19], a modelling tool that estimates the concentration prediction intervals and graphically superimposes these intervals on observed concentrations after a standardised dose, was used to evaluate how well the model predicted the distribution of observed plasma concentrations. Simulation was performed using 1000 subjects with characteristics taken from studied patients.

2.8.3 Use of Priors

The principle of using prior information is that previous data can be used to support a PK model under which the current data are being analysed [20]. The parameters (including their uncertainty) of the model derived from the more informative data are then used to analyse the data in question in the context of prior knowledge. The better the prior knowledge, the more the data under analysis will be constrained to be similar to the prior information. Using prior information is done by augmenting the objective function (a measure of fit) derived from the observed data with a penalty function, which is a summary of data from previous (more informative) studies [21]. Fentanyl priors were sourced from two publications. Loughren and colleagues estimated fentanyl parameters and their variability in a study investigating the impact of St John's wort on pharmacokinetics [22]. Shafer and colleagues estimated fentanyl parameters using pooled data during infusion [23]. Variability was not reported in the article by Shafer and colleagues (Table S1 of the Electronic Supplementary Material [ESM]). Parameter variability estimates for fentanyl [24] were substituted and consequent priors used as a confirmatory analysis for the primary analysis that used priors described by Loughren and colleagues (Table S1 of the ESM). Use of such prior IV information also allowed estimation of the bioavailability of the nasal delivery system.

2.8.4 Compartment Model

A three-compartment linear disposition model with first-order absorption and first-order elimination was used to analyse concentration–time profiles. Others had analysed fentanyl using a three-compartment model and that information was used as priors. The model was parameterised in terms of clearance, intercompartmental clearances (Q_2 and Q_3), three volumes of distribution (V_1, V_2, V_3) and an absorption rate constant. The latter was expressed as an absorption half-time. Intranasal fentanyl bioavailability ($F_{FENTANYL}$) was constrained between 0 and 1 [25], while a logistic distribution was used for its variability to maintain estimates within these limits [26].

2.9 Pharmacodynamic Analysis

The primary pharmacodynamic (PD) outcome measure was the sum of pain intensity difference (SPID) for the time interval from 0 to 180 min after fentanyl administration. The SPID was calculated as weighted sums of the time elapsed since previous assessment and pain intensity difference (PID) at each time point:

$$SPID_t = \sum PID_t \times \left(time_t - time_{t-1} \right) (minute),$$
$$PID_t = PI\ baseline - PI\ time\ (t),$$

where PI is the pain intensity on an 11-point numeric rating scale. For each patient, the value for SPID was converted to a percentage of maximum SPID (%$maxSPID_{0–180}$) by division into the calculated maximum value [27]. Exacerbation of pain was defined as %maxSPID $\geq -33\%$ and that pain at rest was $\geq$ 4/10 and dynamic pain was $\geq$ 6/10 [28]. For an estimate of minimum effective concentration (MEC)

of fentanyl and oxycodone when co-administered, we used the last plasma concentrations obtained before the first rescue oxycodone dose after fentanyl administration.

2.10 Outcome Measures

The primary PK outcome measure was fentanyl exposure, $AUC_{0–180}$ and the primary PD outcome measure was %max-$SPID_{0–180}$ during the first 3 h after fentanyl administration.

2.11 Statistical Analysis

The sample size estimation was based on data presented by Christrup and colleagues [7]. In that study $AUC_{0–180}$ after intranasal fentanyl 100 µg was 48.5 min·ng/mL (standard deviation 10.3) and after fentanyl 200 µg was 77.5 min·ng/mL (standard deviation 24.1). Based on those data, 14 patients would provide a study power over 0.9 at $\alpha = 0.05$ and show a difference for fentanyl exposure between the two dose levels. The appropriateness of sample size was also confirmed for PD comparisons, in the study from Christrup et al. [7], the mean of $SPID_{0–60}$ was 120 (standard deviation 71) for intranasal fentanyl 100 µg and that for fentanyl 200 µg was 252 (standard deviation 66).

SigmaPlot version 13 (Systat software, San Jose, CA, USA) was used for statistical analysis. The comparison of the two dosing groups was done using the Mann–Whitney Rank Sum test. The differences in C_{max} and $AUC_{0–180}$ between 100-µg and 200-µg doses were tested with the Wilcoxon signed rank test. Correlations between patient characteristics and C_{max} or $AUC_{0–180}$ were tested with the Pearson's correlation coefficient. The *r*-values of − 0.29 to + 0.29 were considered to indicate a weak correlation, − 0.49 to − 0.3 or 0.3–0.49 a moderate correlation, − 0.89 to − 0.5 or 0.5– 0.89 a strong correlation, and − 1.0 to − 0.9 or 0.9– 1.0 a very strong correlation. Data are presented as median (minimum–maximum) or number of cases if not otherwise indicated. A *p*-value of ≤ 0.05 was considered significant.

3 Results

3.1 Patient Characteristics

3.1.1 Pharmacokinetic Data

The PK analysis comprised 16 patients with 256 drug assay observations (Table 1). All 224 plasma fentanyl concentrations measured after drug administration were above the LLoQ. A MEC of fentanyl 0.5 ng/mL [29] was achieved in all 16 administrations after intranasal fentanyl 100 µg and in 15 out of 16 administrations after fentanyl 200 µg. Plasma fentanyl concentration was ≥0.5 ng/mL for a median of 25 min (range 11–68 min) after fentanyl 100 µg and 77 min (range 0–180 min) after fentanyl 200 µg, respectively. Raw data are shown in Fig. 2 and the C_{max}, time to C_{max} and $AUC_{0–180}$ from the non-compartmental analysis are presented in Table 2. The C_{max} and AUC_{0-180} values after fentanyl 200 µg were divided by the values observed after fentanyl 100 µg to determine a within-subject comparison (200/100 ratio). Patients ID2 and ID11 in Group 1 showed lower fentanyl exposure after intranasal administration of fentanyl 200 µg on the third postoperative morning than after fentanyl 100 µg on the first postoperative morning (within-subject 200/100 ratio of 0.62 and 0.91). Patients ID6 and ID14 in Group 2 showed similar, unexpectedly low fentanyl exposure after 200 µg of fentanyl on the first postoperative morning compared with the 100 µg of fentanyl dose on the

Table 1 Patient characteristics. Data are presented as the number of patients or median [minimum–maximum]

Parameter	Group 1 Intranasal fentanyl on POD1 100 µg and on POD3 200 µg ($n = 8$)	Group 2 Intranasal fentanyl on POD1 200 µg and on POD3 100 µg ($n = 8$)
Sex (male/female)	7/1	6/2
Age (years)	63 [51–70]	65 [49–67]
Height (m)	1.75 [1.64–1.83]	1.73 [1.64–1.84]
Weight (kg)	72 [59–98]	77 [69–129]
BMI (kg/m^2)	24.2 [19.3–32.4]	28.1 [23.5–41.7]
ASA (II/III/IV)	1/5/2	–/7/1
TBW (L)	43.2 [32.7–56.7]	44.4 [34.2–53.9]
SMM (kg)	27.6 [18.7–37.9]	28.5 [20.6–34.8]
FM (kg)	17.7 [8.7–52.3]	22.7 [12.8–31.7]
VAT (L)	3.3 [1.0–10.8]	2.9 [2.1–5.1]

ASA American Society of Anaesthesiologist's physical status classification, *BMI* body mass index, *FM* fat mass, *POD* postoperative day, *SMM* skeletal muscle mass, *TBW* total body water, *VAT* visceral fat

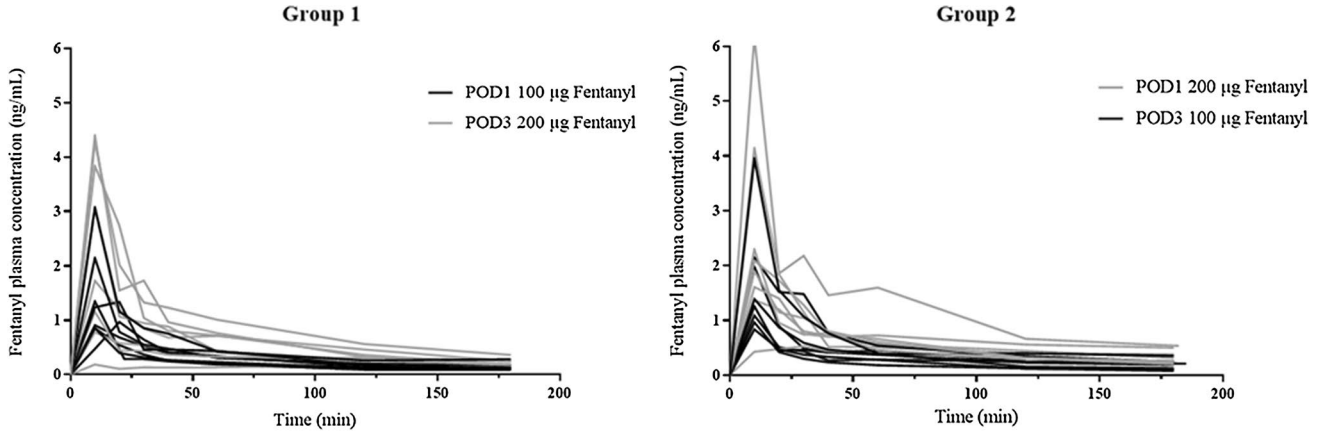

Fig. 2 Fentanyl plasma concentrations after intranasal fentanyl 100 µg and fentanyl 200 µg from two dosing sequences plotted against time. In Group 1, patients ($n = 8$) received 100 µg of intranasal fentanyl on the first postoperative morning and 200 µg on the third postoperative morning and in Group 2 ($n = 8$) vice versa. *POD* postoperative day

Table 2 Pharmacokinetic parameters of intranasally administered fentanyl based on a non-compartmental analysis. In Group 1, patients ($n = 8$) received fentanyl 100 µg on the first postoperative morning and fentanyl 200 µg on the third postoperative morning and in Group 2 ($n = 8$) vice versa

Pharmacokinetic parameters									
		Intranasal fentanyl dose						Within-subject 200/100 ratio	
		100 µg			200 µg				
	ID	C_{max} (ng/mL)	$AUC_{0–180}$ (min·ng/mL)	t_{max} (min)	C_{max} (ng/mL)	$AUC_{0–180}$	t_{max} (min)	C_{max}	$AUC_{0–180}$
Group 1	2	1.4	40.5	10	0.2	25.1	10	0.1	0.6
$n = 8$	4	0.9	37.3	10	3.8	144.3	10	4.5	3.9
	9	0.9	55.2	10	1.7	111.5	10	1.9	2.0
	10	1.0	52.1	20	0.8	58.7	10	0.8	1.1
	11	2.2	71.5	10	1.2	64.9	10	0.5	0.9
	13	1.3	69.0	20	4.4	148.6	10	3.3	2.2
	15	0.9	39.7	10	3.1	103.0	10	3.6	2.6
	16	3.1	103.0	10	4.3	179.8	10	1.4	1.7
Median [minimum–maximum]		1.2 [0.9–3.1]	53.7 [37.3–103.0]	10 [10–20]	2.4 [0.2–4.4]	107.2 [25.1–179.8]	10 [10–10]	1.7 [0.1–4.5]	1.9 [0.6–3.9]
Group 2	1	1.3	68.2	10	1.4	103.1	10	1.1	1.5
$n = 8$	3	1.1	57.2	10	6.2	154.9	10	5.7	2.7
	5	2.0	74.2	10	4.1	224.8	10	2.1	3.0
	6	2.2	112.8	10	0.5	62.9	30	0.2	0.6
	7	1.4	85.5	10	1.6	125.8	10	1.2	1.5
	8	0.8	42.5	10	1.9	103.0	10	2.3	2.4
	12	1.0	38.1	10	2.1	115.1	10	2.2	3.0
	14	4.0	106.0	10	2.3	94.4	10	0.6	0.9
Median [minimum–maximum]		1.3 [0.8–4.0]	71.2 [38.1–112.8]	10 [10–10]	2.0 [0.5–6.2]	109.1 [62.9–224.8]	10 [10–30]	1.6 [0.2–5.7]	2.0 [0.6–3.0]
P-value between groups		0.574	0.234		0.959	0.574		1.0	0.878

$AUC_{0–180}$ area under the plasma concentration–time curve from time zero to time of last quantifiable concentration, *C_{max}* maximum plasma drug concentration, *ID* patient identification number, *POD* post-operative day, *t_{max}* time to reach C_{max} following drug administration

third postoperative morning (within-subject 200/100 ratio of 0.56 and 0.89). This BOV was captured in the population PK analysis (Table 3).

Table 3 Standardised population pharmacokinetic parameter estimates for intranasal fentanyl using Loughren priors [22]

Standardised population pharmacokinetic parameter estimates				
Parameter	Estimate	%BSV	%BOV	95% CI
CL (L/min/70 kg)	0.517	21.1	46	0.199–0.823
Q_2 (L/min/70 kg)	1.06	27.5	–	0.33–1.72
Q_3 (L/min/70 kg)	0.789	41.2	–	0.403–1.169
V_1 (L/70 kg)	31.2	29.9	107	12.2–42.1
V_2 (L/70 kg)	20.1	49.3	–	9.0–29.8
V_3 (L/70 kg)	149	35.6	–	137–157
$T_{abs1/2}$ (min)	1.86	3.2	–	1.10–2.74
F_{NASAL}	0.765	19.7	–	0.414–0.996
Err add (ng/mL)	0.0175	–	–	0.0122–0.0228
Err prop (%)	21.2	–		16.2–23.9

BSV between-subject variability, *BOV* between-occasion variability, *CI* confidence interval of the structural estimate, F_{NASAL} intranasal bioavailability, $T_{abs1/2}$ absorption half-life

A three-compartment linear disposition model with first-order absorption and first-order elimination was used to analyse concentration–time profiles. Population estimates of clearance (CL), intercompartmental clearances (Q_2 and Q_3) and three volumes of distribution (V_1, V_2, V_3), respectively, standardized to a 70-kg person using allometric models

Residual unidentified variability was described by combined proportional and additive residual error model for each observation prediction (Err prop, Err add)

Pharmacokinetic parameters are listed in Table 2. A non-compartment analysis demonstrated dose proportionality with C_{max} and $AUC_{0–180}$. In all patients ($n = 16$), the median C_{max} after fentanyl 100 µg was 1.3 ng/mL and the median $AUC_{0–180}$ was 62.7 min·ng/mL and after fentanyl 200 µg was 2.0 ng/mL (compared to 100 µg $p = 0.109$) and 107.3 min·ng/mL ($p = 0.007$), respectively.

Compartmental parameter estimates for the fentanyl three-compartment analysis using Loughren priors [22] are shown in Table 3 and those for the confirmatory analysis using Shafer et al. priors [23] in Table S2 of the ESM. Figure 3 shows satisfactory visual predictive check plots for these PK data. In a body composition review, C_{max} and $AUC_{0–180}$ correlated inversely with total body water, skeletal muscle mass and visceral fat, but not with fat mass (Table S3 of the ESM).

3.1.2 Pharmacodynamic Data

The pain scores in the two groups are presented in Fig. 4. The median %maxSPID after fentanyl 100 µg on the first postoperative morning in Group 1 was at rest 11% (− 44% to 86%), during deep breathing 30% (5–81%), and at cough 25% (0–70%), and after fentanyl 200 µg on the third postoperative morning at rest 73% (0–97%), during deep breathing 49% (− 44% to 97%) and at cough 23% (−19% to 56%).

In Group 2, the median %maxSPID on the first postoperative morning after fentanyl 200 µg was at rest 57% (− 261% to 97%, $p = 0.259$ compared to Group 1), during deep breathing 53% (− 4% to 81%, $p = 0.279$) and at cough 29% (− 102% to 67%, $p = 1.000$), and after fentanyl 100 µg on

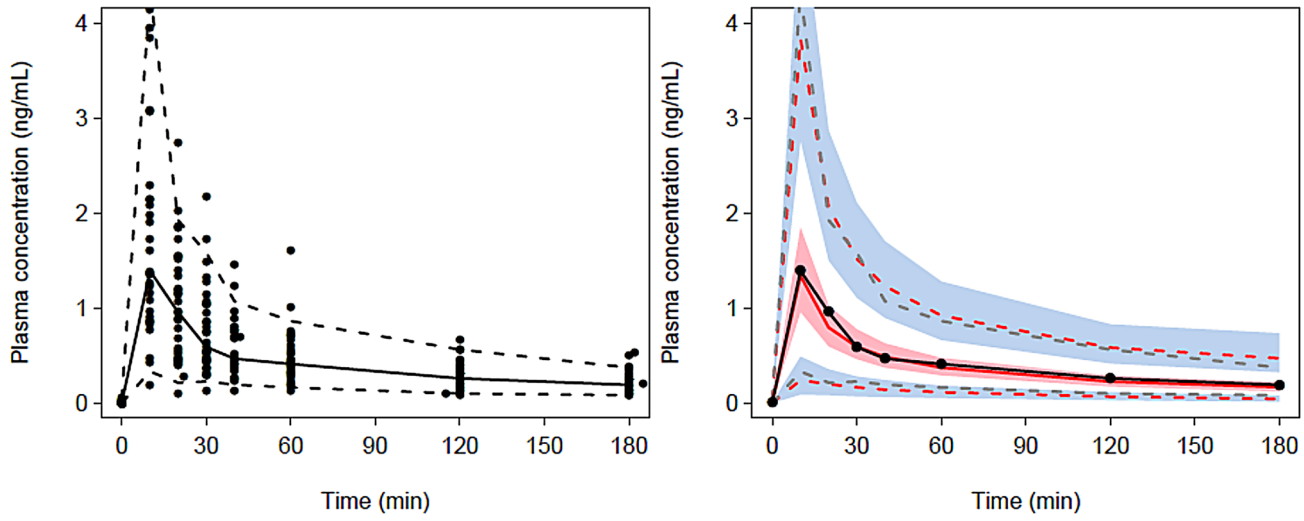

Fig. 3 Visual predictive check for the fentanyl pharmacokinetic model. All plots show median and 90% intervals (solid and dashed lines).The left-hand plot shows all prediction-corrected observed concentrations. The right-hand plot shows percentiles (10%, 50% and 90%) for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (shaded areas)

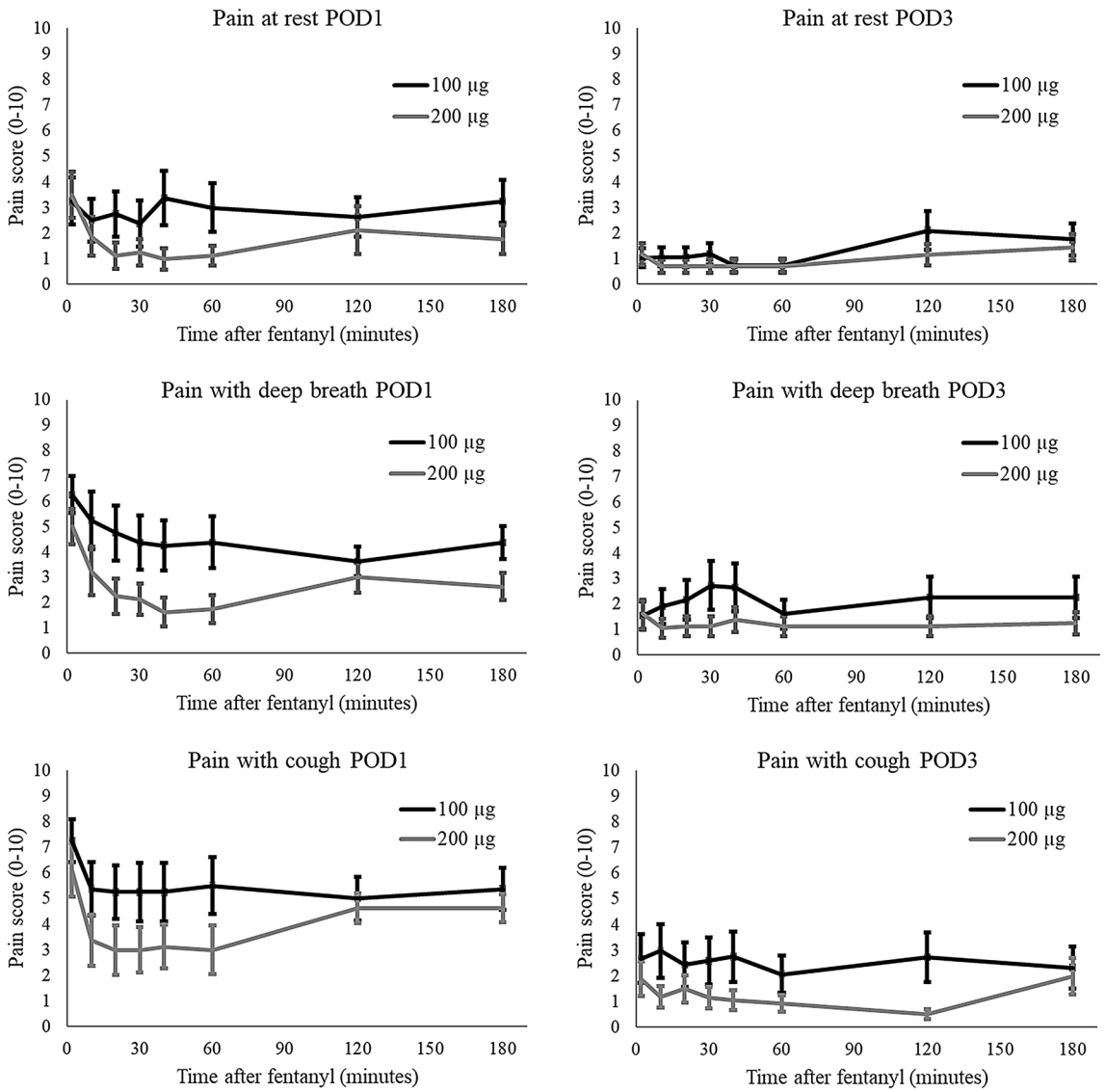

Fig. 4 Pain scores on the first and third postoperative day (POD) during the first 3 h after intranasal administration in the two groups, in group 1 (n = 8) intranasal fentanyl 100 µg was administered on the first postoperative morning before chest tube removal and intranasal fentanyl 200 µg on the third postoperative morning, and in group 2 (n = 8) vice versa. Pain was assessed with an 11-point numerical rating scale (0 = no pain, 10 = most pain) at rest, with deep breathing and with cough. Data are mean with the standard error of the mean

the third postoperative morning at rest 0% (− 27% to 97%, p = 0.189), during deep breathing 80% (− 165% to 97%, p = 0.336) and at cough 2% (− 75% to 80%, p = 0.328).

To compare our PD data with that of Chistrup and colleagues [7] in a post hoc analysis, we calculate $SPID_{0–60}$ for pain at cough. The mean $SPID_{0–60}$ was 134 (standard deviation 117) after fentanyl 100 µg and that after fentanyl 200 µg was 182 (standard deviation 103), respectively.

Before the first intranasal fentanyl administration on the first postoperative morning, the patients in Group 1 had received 27 mg (10–34) IV oxycodone compared to 30 mg (25–56) in Group 2 (p = 0.195), and before the second fentanyl dose on the third postoperative morning in Group 1 77 mg (42–201) compared to 85 mg (53–131) IV oxycodone in Group 2 (p = 0.950). The median plasma oxycodone concentration before the first fentanyl administration was 25.4 ng/mL (11.7–41.5) in Group 1 and 34.1 ng/mL (17.6–39.5, p = 0.372) in Group 2, and before the second fentanyl administration in Group 1 was 24.7 ng/mL (10.0–45.6) and 20.5 ng/mL (6.7–67.1, p = 0.912) in Group 2, respectively.

On the first postoperative morning, four patients in Group 1 (fentanyl 100 µg) were administered seven oxycodone doses via a PCA pump during the first 180 min after fentanyl administrations, the median time to the first rescue dose was 81 min (36–120), compared to six patients in Group 2 (fentanyl 200 µg) with seven oxycodone doses and the

median time to the first dose was 148 min (45–176) [p = 0.067], respectively. On the third postoperative morning, five patients in Group 1 (fentanyl 200 µg) were administered six oxycodone doses via a PCA pump during the first 180 min after fentanyl administrations, the median time to the first dose was 108 min (52–172), and three patients in Group 2 (fentanyl 100 µg) administered seven PCA-oxycodone doses, the median time to the first dose was 54 min (32–117) [p = 0.393].

The median oxycodone concentration in the preceding blood sample before rescue oxycodone administrations (an estimate of MEC) was 17.7 ng/mL (8.9–33.9) on the first postoperative morning and 11.7 ng/mL (5.2–34.7) on the third postoperative morning, and those for fentanyl 0.31 ng/mL (0.19–0.73) and 0.36 ng/mL (0.16–0.76), respectively.

Four patients had six adverse effects related to fentanyl administration. One patient had nausea and vomiting 30 min, and confusion 6 h after fentanyl 200 µg. One patient had nausea 5 h after fentanyl 200 µg and another 3.5 h after fentanyl 100 µg. One patient had constipation 28 h after fentanyl 100 µg.

4 Discussion

Our data support the use of transmucosal fentanyl for incidental breakthrough pain after cardiac bypass surgery during the first postoperative days. Absorption PK parameter estimates (intranasal bioavailability 0.77, absorption half-time < 2 min) support early analgesic responses and are consistent with those reported in younger healthy adults [7, 30]. The $AUC_{0–180}$ and C_{max} were dose proportional, and a MEC of fentanyl 0.5 ng/mL observed in patients scheduled for surgical procedures involving an abdominal incision [29] was reached in almost all (97%) of the patients given intranasal fentanyl 100 µg or fentanyl 200 µg.

We analysed data using both linear compartmental and non-compartmental pharmacokinetics. Priors were used to better characterise absorption parameters (intranasal bioavailability, absorption half-time). Although priors differ for some parameter estimates (e.g., Shafer et al. [23] use infusion data to estimate a bigger V3), absorption parameters were similar in both analyses. In the present study, there were low within-subject 200/100 ratios in fentanyl exposure in 4 of 16 participants, consistent with the large BOV noted for clearance estimates and BSV for bioavailability. The nasal route is known to be associated with high BSV and BOV, much of which is attributable to absorption dependent on the anatomy and physiology of this mucosal surface [31]. However, this variability is accounted for by titration of opioids to effect and intranasal fentanyl, with its rapid absorption, is easy to re-dose if the anticipated effect is not achieved after the initial dose. The clinical utility of intranasal fentanyl administration was supported by observed analgesic effect: no pain exacerbations were observed during chest tube removal or during physiotherapy and $\%maxSPID_{0–180}$ values after intranasal fentanyl were positive in the majority of patients. Our current analysis indicates intranasal fentanyl 100 µg as an initial dose in the management of incidental breakthrough pain in cardiac surgery patients. In this current study, early pain after cardiac bypass surgery was similar to that reported by others but the pain resolution was faster [32] using intranasal fentanyl for breakthrough pain.

Pain intensity differences for 0–60 min were similar to those reported by Christrup and colleagues [7] in patients undergoing third-molar extraction with intranasal fentanyl 100 µg and 200 µg. Veldhorst-Janssen et al. [33] have shown that a lower dose of intranasal fentanyl 50 µg 10 min before drain removal in surgery patients was insufficient for effective analgesia. In that study, a two-fold increase in pain scores was recorded during drain removal and this response was similar to that observed in patients administered intranasal placebo. The mean C_{max} fentanyl concentration was 0.22 ng/mL, similar to that reported in a parturient woman after a single intranasal fentanyl 50-µg dose [8]. These concentrations are two- to three-fold less than the MEC of fentanyl 0.5 ng/mL [29].

Intranasal fentanyl in this current study was effective at both doses and the analgesic action was two-fold longer with the higher fentanyl 200-µg dose. The duration of effect of fentanyl 100 µg before the need for oxycodone of 1.1 h was similar to that in Christrup et al. (1.0 h), but with fentanyl 200 µg, the effective duration of 2.1 h was half an hour longer than that reported in patients who had undergone third-molar extraction [7]. It should be noted that in the present study fentanyl was co-administered with oxycodone. Before fentanyl administration, the mean oxycodone plasma concentrations were 29 ng/mL on the first postoperative morning and 26 ng/mL on the third postoperative morning, these oxycodone concentrations are similar to the MEC reported in patients with abdominal surgery [34–36].

When we compared the oxycodone concentrations after fentanyl administrations and before the next PCA oxycodone doses (our estimate of MEC) to others who have estimated MEC, it was noted that the median oxycodone values of 18 ng/mL on the first postoperative morning and 12 ng/mL on the third postoperative morning are two to three-fold higher than those reported by Pesonen and colleagues [37] also in cardiac surgery patients. In both studies, the estimates of MEC of fentanyl were similar to those reported earlier in abdominal surgery patients [29]. It is likely that differences in the study designs have contributed to discrepancies, in the current study, assay samples were collected during activities known to be painful, while Pesonen and colleagues report rescue oxycodone use while patients were lying in bed. Our

data indicate that MEC values for dynamic pain are substantially higher than those for pain at rest. This is supported by Cajanus and colleagues [38] who have shown that in breast surgery patients an oxycodone MEC value, when administered after fentanyl, was increased by 21% per one-point increase in the dynamic pain intensity score. However, the MEC concentrations obtained in the current study for oxycodone before fentanyl were similar but after fentanyl are substantially lower than those reported in abdominal surgery patients with no concomitant fentanyl. In cholecystectomy and midline laparotomy patients where remifentanil infusion was used for intraoperative analgesia, postoperative MECs of oxycodone 20–30 ng/mL were reported [34–36].

The pain model used in the present study, chest tube removal and postoperative physiotherapy are clinically relevant to test the effectiveness of intranasal fentanyl in this patient population. Cardiac bypass surgery patients are exposed to several painful procedures during the first days of recovery and among the most painful and distressing procedures are chest tube removal, turning in the bed, respiratory exercises and mobilisation [32, 39, 40]. In the present study, pain scores were recorded both at rest and during activity and were highest during coughing. That was expected as coughing generates excessive force up to 270 N that is an over ten-fold higher force than commonly used in these types of analgesic studies [29, 34–36, 41]. The assessment of dynamic pain is important, as severe pain negatively affects function, physical activity and deconditioning after surgery. Deep breathing and coughing are essential to reduce pulmonary complications and early mobilisation reduces the hospital length of stay [42].

Fentanyl has a high extraction ratio [43] and thus clearance may be impaired with decreased hepatic blood flow consequent to low cardiac output [44]. In the present study, there were no cases of low cardiac output. Moreover, population clearance was similar to that reported by others [7] and there were no obvious outliers, and thus it is unlikely that surgery or a cardiac bypass has affected that much the PK parameters obtained.

The intranasal fentanyl delivery system can administer an inaccurate dose if not used in an optimal manner. This has probably contributed to low observed fentanyl plasma concentrations and intranasal bioavailability variability. The device contains only a small amount of liquid and if the device is tilted too much, the tube inside the device may not reach liquid content and the spray will not provide the intended amount of fentanyl. Our hospital pharmacy was responsible for covering the bottle with opaque tape, thus the delivery mechanism could not be checked during drug dosing, although the intention was to keep the device in an upright position. However, these types of dosing errors were less likely as the patients were able to feel the spray in their nostril and all the administrations were performed by the same investigator who had extensive training with placebo devices before the study. Moreover, the fentanyl exposure of subjects in the present study was similar or higher than that reported by others [7].

5 Conclusions

Our data support the feasibility of transmucosal fentanyl for incidental breakthrough pain in cardiac surgery patients during the first postoperative days. There was no exacerbation of pain after intranasal fentanyl 100-µg and 200-µg administration 10 min before painful procedures, and thus 100 µg should be an appropriate starting dose. As a novel finding, C_{max} and fentanyl exposure correlated inversely with skeletal muscle mass, total body water content and visceral fat.

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Declarations

Conflicts of interest Antti Valtola, Maisa Laakso, Henriikka Hakomäki, Brian J. Anderson, Hannu Kokki, Veli-Pekka Ranta, Valtteri Rinne and Merja Kokki have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study protocol was approved by the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland (Ref. 657//2018), had institutional approval and was performed in accordance with the Declaration of Helsinki.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors' contributions Principal investigator: Merja Kokki.

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