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Comparison of fentanyl iontophoretic transdermal system and routine care with morphine intravenous patient-controlled analgesia in the management of early postoperative mobilisation: results from a randomised study

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Abstract

Introduction: Fentanyl iontophoretic transdermal system (ITS) (IONSYS®, The Medicines Company, Parsippany, NJ, USA) and morphine intravenous (IV) patient-controlled analgesia (PCA) have demonstrated equivalent pain control in several published studies. The primary objective of the current study was to compare fentanyl ITS with morphine IV PCA with regard to the patient's ability to mobilise with acute postoperative pain.

Methods: In this multicentre, open-label, randomised, active-controlled, prospective phase IV study, postoperative patients initially received IV morphine and were titrated to pain score ≤ 4 out of 10 on a Numeric Rating Scale (NRS) and then received fentanyl ITS (up to 240 μg (6 doses)/hour; up to a maximum of 3.2 mg (80 doses)/24 hours) or morphine IV PCA (doses up to 20 mg morphine/2 hours, up to 240 mg/24 hours). The primary efficacy measure was ability to mobilise, assessed using patient responses to three validated questions regarding mobility on a 6-point Likert scale (0 = no difficulty to mobilise to 5 = a very great deal of difficulty to mobilise). The study was originally planned to include ~200 patients. However, following the early suspension and termination of the study, a total of 108 patients were randomised to study treatment.

Results: One hundred and eight patients were recruited prior to undergoing surgical procedures (orthopaedic surgical procedures (72%) or underwent major abdominal procedures (28%)). Postoperatively, 58 were randomised to receive fentanyl ITS, and 50 to morphine IV PCA. Fentanyl ITS patients had a greater ability to mobilise at the time of stopping study drug, with an adjusted mean ability to mobilise score (95% confidence interval (CI)) of 0.14 (−0.19, 0.47) for fentanyl ITS patients and 2.37 (1.98, 2.76) for morphine IV PCA patients ($p < 0.001$).

Conclusion: Patients treated with fentanyl ITS reported that they were better able to mobilise than patients treated with morphine IV PCA, at all time-points following surgery out to 24 hours.

Keywords

Fentanyl, iontophoretic transdermal system, morphine, patient-controlled analgesia, postoperative mobilisation

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Introduction

Effective postoperative pain management is a critical component of contemporary accelerated recovery. Inadequate management of acute postoperative pain is associated with a range of well-recognised postoperative complications such as cardiac complications, atelectasis and chest infection, deep vein thrombosis, delayed wound healing, prolonged ileus, muscle atrophy, negative impact on sleep and mood and in the longer term, persistent (chronic) postoperative pain.^{1–4} In addition to reduced patient satisfaction, these negative physiological outcomes of poorly managed postoperative pain may result in impaired rehabilitation and delayed hospital discharge and/or hospital readmission, adding to healthcare costs.^{2,3,5,6}

Patient-controlled analgesia (PCA) is an effective alternative to intermittent nurse administered doses, permitting the patient to access pain relief on-demand using a programmed delivery device; however, such systems require skilled set-up and supervision, and even when trained staff are available, the hazards of possible overdose or system failure remain.⁷ Pain management practices must therefore balance the analgesic needs of the patient with safety issues associated with either inadequate analgesia or the dangers of opioid overdose.

Studies have shown that intravenous PCA (IV PCA) with morphine, the most commonly administered analgesic modality for the treatment of acute moderate to severe postoperative pain, is more effective than intramuscular administration.⁸ Traditional IV PCA machines require a staff-programmed pump, which, due to its bulk and IV connection, can limit patient mobility and introduces the potential for drug and dosing errors as a result of incorrect set-up and programming.^{9–11} Although rare, the consequences of programming errors can be serious and may include death.^{7,9,12,13}

The fentanyl iontophoretic transdermal system (ITS) (IONSYS®, The Medicines Company, Parsippany, NJ, USA) delivers a fixed dose (40 µg) of fentanyl transdermally using the principle of iontophoresis (Figure 1). The system is battery-driven, pre-programmed, needle-free, self-contained within a compact plastic housing and fully disposable at the end of its 24-hour or 80-dose lifespan. Thus, fentanyl ITS requires less investment of skilled staff time to set up and trouble-shoot than IV PCA,¹⁴ is not associated with the risk of line occlusion and displacement issues seen with IV PCA cannulae and, being a single-use disposable device, is a low cross-contamination hazard. However, it is important to note that patients treated with fentanyl ITS still require skilled nursing monitoring.

Four pivotal studies evaluating morphine IV PCA and fentanyl ITS have shown comparable analgesic

Figure 1. Diagram of fentanyl iontophoretic transdermal system.

efficacy across a variety of surgical patient groups, including abdominal hysterectomy, upper and lower abdominal surgery (undifferentiated) and single knee and single hip replacement surgeries using a non-inferiority model with the validated patient global assessment (PGA) questionnaire as the primary outcome variable.^{15–18} Three of the four pivotal studies^{16–18} utilised the validated Nurse Ease-of-Care (EOC) questionnaire.¹⁹ Pooled analyses (N = 1882) were conducted to evaluate patient mobility from these three studies.²⁰ The difference of the overall and individual mobility scores in this pooled analysis favoured fentanyl ITS over morphine IV PCA ($p < 0.001$). Two of the four pivotal trials included physical therapy rating of mobility via the Physical Therapy EOC questionnaire with three questions regarding the patient transferring to a chair, ambulating around in a room and ambulating outside of the room. In these studies, physical therapists also favoured fentanyl ITS compared to morphine IV PCA for each of the three mobility items ($p < 0.001$).

Enhanced recovery after surgery (ERAS) protocols are designed to achieve early recovery by reducing metabolic stress caused by surgery and by rapidly returning patients back normal activities.²¹ One of the key features of most ERAS protocols is early mobilisation, and therefore, the use of pain delivery systems that permit patients to mobilise early is very important.

The time taken for a patient to mobilise is also a key indicator of the patient's fitness to be discharged from hospital. The primary objective of this study was to evaluate fentanyl ITS and morphine IV PCA with regard to the patient's ability to mobilise during the management of acute moderate to severe postoperative pain in patients who had undergone elective major abdominal (abdominal hysterectomy) or orthopaedic surgery (unilateral primary total hip arthroplasty).

Materials and methods

This was a multicentre, randomised, open-label, active-controlled, parallel-group, prospective Phase IV study conducted at seven centres in the United Kingdom. Written informed consent was obtained from all potential subjects prior to any study procedure being performed. The study was conducted between 16 May 2008 and 29 September 2008 with Institutional Review Board/Independent Ethics Committee approvals prior to screening subjects. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines. The study was suspended early and then terminated due to concerns regarding one batch of the study drug used outside of this study, given the likely substantial delay until the study could be resumed, which could have affected the continuity of the results. With the original fentanyl ITS system, there was the potential for development of condensation leading to corrosion of the electronics. With the original system, the corrosion on the printed circuit board could have potentially resulted in self-initiation even though there were no known instances of self-initiations.²² Therefore, the system was withdrawn from the market and redesigned. The currently marketed system is the second generation fentanyl ITS and was designed to separate the hydrogels in the Drug Unit from the electronic circuit of the Controller during manufacture and storage, removing the primary cause of corrosion and thereby improving reliability.²³

Subjects

Patients were screened and recruited if they were at least 18 years of age and planned to have their anticipated acute moderate to severe postoperative pain managed with parenteral opioids by PCA, for at least 24 hours after an elective major abdominal (abdominal hysterectomy) or orthopaedic surgery (unilateral primary total hip arthroplasty). Informed consent was obtained prior to any study-related procedures. The investigators provided information and the opportunity to discuss postoperative pain, the pain assessments and goals for pain control. Following surgery, while recovering from general, spinal or epidural anaesthesia in the recovery room (post-anaesthesia care unit (PACU)), the staff titrated the patient (once alert) with IV morphine, as required, to a level of comfort Numerical Rating Scale (NRS) score of ≤ 4 (where 0 = no pain and 10 = worst possible pain). At this stage,

the final screening procedure was conducted to determine whether the patient was eligible to continue in the study, including NRS score of ≤ 4 . Patients were excluded if >6 hours had elapsed since the patient arrived in the recovery room. Patients meeting all entry requirements were then randomised to receive either fentanyl ITS or morphine IV PCA.

Dosage and administration

Fentanyl ITS. Each needle-free system delivered 40 μg fentanyl per on-demand dose up to a maximum of 240 μg (6 doses each of 10 minutes duration) per hour but not more than a maximum of 80 doses within 24-hour period. Fentanyl ITS is applied to intact, non-irritated, non-irradiated skin on the chest or upper, outer arm. A virtually imperceptible low-intensity electric current is used to drive the positively charged fentanyl molecules from the system anode through the skin's stratum corneum into the subcutaneous space, from which they diffuse into the circulatory system. The system operates for up to 24 hours or 80 dose deliveries, whichever comes first, and then becomes inoperative. If required, the ITS was replaced every 24 hours, or earlier if the patient had used 80 doses in less than 24 hours.

Morphine IV PCA. Morphine sulphate was infused intravenously by a PCA pump using set bolus doses with a fixed lock-out period. The size of the bolus dose and duration of the lock-out period could vary with local routine clinical practice, up to a maximum total of 20 mg morphine per 2 hours for the duration of the treatment. The set-up and operation of the PCA pump was in accordance with standard practice in each study centre. Where possible, the placement of the IV line access site was in the non-dominant lower arm or hand.

Supplemental opioid co-medication. Patients were permitted to be treated with supplemental opioids in the form of parenteral morphine sulphate (supplied by each study centre) for the first 3 hours. Patients requiring additional opioid analgesics after the first 3 hours post-randomisation were discontinued from the study due to inadequate analgesia; however, they were still included in the intention-to-treat (ITT) population. All supplemental opioids were administered by either recovery or ward nurses.

Non-opioid co-medication. Patients could receive non-opioid analgesics as part of a multimodal regimen (including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and/or specific cyclooxygenase inhibitors) intra-operatively or during the postoperative screening or treatment period, according to clinical judgement and institutional practice.

Efficacy assessments

Primary. The primary efficacy endpoint was the patients' evaluation of their ability to mobilise at the time the patient stopped study drug (i.e. fentanyl ITS or morphine IV PCA). This was assessed through the average score of the following three validated questions: (1) because of this system/device, I had to be careful when I used my hands or arms (to eat, brush teeth or sit up in bed); (2) the system/device made it difficult for me to adjust my position in bed; and (3) the system/device interfered with my ability to get out of bed and walk around (to chair in room, to bathroom in room/ward, to hallway). The three items were each scored on a 6-point Likert scale, ranging from not difficult at all (score 0) to a very great deal of difficulty (score 5). The three items were extracted from the validated Patient EOC Questionnaire.²⁴ Assessments were completed hourly during the first 6 hours. If the patient was still receiving study treatment, further assessments were made at 8, 12, 24, 48 and 72 hours after application of fentanyl ITS or enablement of the morphine IV PCA device. Assessments were also made when the patient was fit for discharge (FFD). Investigators discontinued study treatment if there was no further need for parenteral opioid therapy, or they considered that for safety reasons it was in the patients' best interest.

Secondary. The Nurse EOC is a validated questionnaire that has 22 items and covers three broad areas of care delivery associated with acute care pain management systems (i.e. time-consuming, bothersome and satisfaction).¹⁹ Items are scored on a 6-point Likert scale, ranging from not at all to a very great deal of difficulty. The Nurse EOC questionnaire was completed by all recovery room nurses who had experience with the study patient, and thereafter, at the end of each shift, by all ward nurses who had experience with the study patient. If the patient discontinued study treatment, withdrew from the study or was considered FFD, the final Nurse EOC questionnaire was completed at that time.

Pain intensity experienced by the patient was assessed by means of a verbally administered 11-point NRS (0 = no pain; 10 = worst possible pain). The NRS was completed at the same time-points as the three validated questions for the primary endpoint were asked. Five minutes prior to each pain assessment, patients with major abdominal surgery were prompted to take a deep breath and cough.

The PGA of the method of pain control was collected at the end of study treatment. The patient responded to the following question: Overall, would you rate this PCA method of pain control as being poor, fair, good, or excellent?

Patients were assessed for their FFD, according to usual medical and nursing criteria, after application of fentanyl ITS or the enablement of morphine IV PCA. Assessments were hourly during the first 6 hours, and further assessments were made at hours 8 and 12. There was no expectation that a patient would meet FFD during the first 12 hours; this was used as a study assessment tool only. Starting on the first postoperative day, and continuing until the patient was considered FFD, assessments were made at least four times during the day at 4-hour intervals starting in the morning as soon as practicable after the patient had woken. FFD was assessed by the patient fulfilling the following criteria: (1) retaining fluids and food, (2) passing urine without the aid of a catheter, (3) bowel sounds and/or opening, (4) cardiovascular stability, (5) respiratory stability, (6) no postoperative wound complications, (7) pain adequately controlled with oral analgesia only and (8) adequately mobile according to locally acceptable standards for mobility for surgery type and pre-operative expectations. FFD criteria were assessed by the investigator or nursing staff and answered on a Yes or No basis. The secondary endpoint was the 'time to FFD'.

The total dose of morphine used as supplemental opioid medication given between 0–3 hours was evaluated for each patient.

Safety assessments

Safety was assessed by spontaneously reported treatment-emergent adverse events (TEAEs, defined as adverse events (AEs) that occurred on or after the study medication was initiated), vital signs monitoring and non-routine events. The number of doses, strength and specific amount of antiemetics were recorded for each patient.

Statistics

Randomisation and blinding. A computer-generated schedule was prepared before the study to randomise 200 patients to one of the two treatment groups in a 1:1 ratio. The randomisation was balanced and used randomly permuted blocks and stratified by surgery type. The study was not blinded so the randomisation codes were supplied to the study centres with individual patient randomisations in sealed envelopes which remained unopened until the patients completed screening assessments and were deemed eligible for the study.

Populations. An ITT population, including all randomised patients who used the study treatment at least once and who had at least one efficacy measure after system application or device enablement (0 hours),

split by treatment group, was used to assess efficacy. The safety population includes all randomised patients who received treatment.

Efficacy analysis. The primary efficacy endpoint is the patient's evaluation of their ability to mobilise at the time of study discharge, calculated as the mean score of three validated questions. An analysis of covariance (ANCOVA), adjusted for treatment, surgery type and centre, was used to assess mobilising ability difference between treatments. The least squares (LS) means and associated 95% confidence intervals (CIs) are presented for each treatment group. In addition, the estimated difference between the treatment groups with the 95% CI of the difference with the associated p-value is presented. For the patient's pain rating (NRS), the p-value was calculated from an ANCOVA with centre, surgery type and treatment included in the model for ratings completed at 24 and 48 hours. For the NRS at study discharge, the p-value was calculated from an ANCOVA with centre, treatment and treatment duration included as covariates in the analysis. For the Nurse EOC ratings (including total and subsections), the p-value was calculated from an ANCOVA with centre, surgery type and treatment included in the model. Mantel-Haenszel chi-squared test was performed to compare the categories of the PGA of pain control.

A log-rank test, stratified for surgery type, assessed time to FFD and Kaplan-Meier curves presented time to actual discharge. Treatment-emergent AEs were summarised by preferred term.

Sample size calculation. It was assumed that the mean difference in ability to mobilise between treatment groups would be 0.75 at 24 hours, with a common standard deviation (SD) of 1.5. Assuming a two-sided, 5% significance level with 90% power and a dropout rate of 8%, the sample size required was 200 patients, 100 per group. Mobility data from a study comparing fentanyl ITS and morphine IV PCA was non-normal,¹⁸ so the sample size was based on a Mann-Whitney rank-sum test. The observed mean difference in ability to mobilise between treatment groups was -1.182, with a common SD of 0.997, based on data for 72 hours for mixed surgery types, so more conservative treatment difference estimates and common SD were assumed for this sample size calculation.

Results

Subjects

A total of 108 patients were randomised to study drug (58 to fentanyl ITS and 50 to morphine IV PCA), and

of those, 101 completed the study and completed study drug (Figure 2).

Demographic and baseline characteristics were similar between patients in the fentanyl ITS and the morphine IV PCA groups (Table 1). The majority were female (61.1%) and Caucasian (97.2%). Mean age of patients was 58.7 years of age. The majority (72.2%) of patients had orthopaedic surgery.

Efficacy

The LS mean (95% CI) of patient ability to mobilise score at the time patients stopped study drug was 0.14 (-0.19, 0.47) for fentanyl ITS patients and 2.37 (1.98, 2.76) for morphine IV PCA patients (Figure 3). The adjusted mean difference (fentanyl ITS - morphine IV PCA) with 95% CI was -2.23 (-2.55, -1.91), with a p-value of <0.001 from the ANCOVA showing a statistically significant better ability to mobilise for fentanyl ITS, at the time the patient stopped study drug. The 'ability to mobilise' score at all time-points up to 24 hours was better for fentanyl ITS patients than for morphine IV PCA patients (Figure 4). Patients were required to stay in the study for 24 hours, and it was optional after that time-point; therefore, as expected, there were too few patients evaluated at the 48-hour (11 fentanyl ITS and 3 morphine IV PCA) and 72-hour (1 fentanyl ITS and 0 morphine IV PCA) time-points to justify statistical testing.

Patients in the fentanyl ITS group had a significantly lower (i.e. better) total score for the Nurse EOC questionnaire ($p < 0.001$, Table 2).

At 24 and 48 hours, the patients' pain rating was lower, although not statistically significant, for fentanyl ITS patients (Table 2).

Thirty-one fentanyl ITS patients (53.4%) and 19 morphine IV PCA patients (38.8%) gave a response of 'excellent' on the PGA of pain control. The odds ratio (95% CI) comparing fentanyl ITS and morphine IV PCA was 1.81 (0.84, 3.92).

Fifty-four fentanyl ITS patients (93.1%) and 50 morphine IV PCA patients (100.0%) achieved FFD. The median (95% CI) time to FFD was 70.08 hours (65.50-72.25 hours) for fentanyl ITS patients, and 71.21 hours (67.42-90.77 hours) for morphine IV PCA patients ($p = 0.342$). Study drug was stopped due to inadequate analgesia prior to reaching FFD in the four fentanyl ITS patients who did not achieve FFD. When the analysis was repeated by surgery type, by centre and by both centre and surgery type, there were no differences in time to FFD between fentanyl ITS and morphine IV PCA patients.

A total of 12 patients (11.0%) required supplemental morphine in the first 3 hours post-randomisation (10 patients (17.2%) in the fentanyl ITS group and 2

Figure 2. Flow diagram.

ITS: iontophoretic transdermal system, IV: intravenous, PCA: patient controlled analgesia.

(4.0%) in the morphine IV PCA group). The odds ratio (95% CI) comparing fentanyl ITS and morphine IV PCA was 5.00 (1.04, 24.03), showing a statistically significant difference ($p = 0.029$) in the number of patients receiving supplemental morphine post-randomisation, with fentanyl ITS patients more likely to receive supplemental morphine.

The mean number of doses of supplemental morphine required in the first 3 hours post-randomisation was 2.0 (SD = 1.7, range: 1–6) for fentanyl ITS patients and 1.0 (range: 1–1) for morphine IV PCA patients. The adjusted mean amount of morphine required (95% CI) was 9.0 mg (4.5–13.5 mg) for fentanyl ITS patients and was 7.2 mg (–2.6 to 17.0 mg) for morphine IV PCA patients. The adjusted mean difference (fentanyl ITS – morphine IV PCA) with 95% CI was

1.8 (–6.8 to 10.5), which was not statistically significant ($p = 0.624$).

In total, 55 patients (51.0%) used concomitant antiemetic medication during the study (29 fentanyl ITS patients (50.0%) and 26 morphine IV PCA patients (52.0%)). Overall, there were no discernible differences in the use of concomitant antiemetic medication between the two treatment groups. The most commonly used (≥ 10 patients in either treatment group) were cyclizine and ondansetron.

Forty-eight fentanyl ITS (82.8%) and 36 morphine IV PCA patients (72.0%) received postoperative non-opioid analgesics ($p = 0.180$). Thirty-nine fentanyl (67.2%) and 28 morphine IV PCA patients (56.0%) received postoperative paracetamol ($p = 0.230$). Thirty-one fentanyl (53.4%) and 20 morphine IV PCA

Table 1. Patient demographics and baseline characteristics (ITT Population).

	Fentanyl ITS (N = 58)	Morphine IV PCA (N = 50)
Age (years), mean (SD)	58.4 (12.1)	58.9 (11.8)
Female, n (%)	33 (56.9)	33 (66.0)
Caucasian, n (%)	57 (98.3)	48 (96.0)
Body mass index, n (%)		
20–30 kg/m ²	32 (55.2)	30 (60.0)
30–40 kg/m ²	25 (43.1)	18 (36.0)
>40 kg/m ²	1 (1.7)	1 (2.0)
ASA status, n (%)		
I (no disturbance)	12 (20.7)	14 (28.0)
II (mild to moderate systemic disturbance)	46 (79.3)	36 (72.0)
III to V (severe disturbance or greater)	0	0
Type of surgery, n (%)		
Abdominal	17 (29.3)	13 (26.0)
Orthopaedic	41 (70.7)	37 (74.0)
Method of anaesthesia		
General	18 (31.0)	17 (34.0)
Spinal (<4 hours duration of action)	39 (67.2)	33 (66.0)
Epidural (single administration only)	1 (1.7)	0
Concomitant medications		
Number of patients receiving concomitant medications	56 (96.6)	50 (100.0)
Medications with ≥15% in either treatment group		
Acetylsalicylic acid	9 (15.5)	12 (24.0)
Cefuroxime	14 (24.1)	17 (34.0)
Cyclizine	20 (34.5)	20 (40.0)
Diclofenac	28 (48.3)	15 (30.0)
Dihydrocodeine	6 (10.3)	8 (16.0)
Enoxaparin	12 (20.7)	12 (24.0)
Lactulose	3 (5.2)	11 (22.0)
Morphine	10 (17.2)	6 (12.0)
Ondansetron	12 (20.7)	12 (24.0)
Panadeine Co.	11 (19.0)	10 (20.0)
Paracetamol	36 (62.1)	23 (46.0)
Senna Alexandrina	7 (12.1)	13 (26.0)
Tramadol	26 (44.8)	31 (62.0)

ITS: iontophoretic transdermal system; ITT: intent-to-treat; IV: intravenous; N: number of patients in the analysis set; n: number of patients in the category subgroup; PCA: patient-controlled analgesia; SD: standard deviation.

Figure 3. Ability to mobilise at the time the patient stopped study drug (ITT Population).

CI: confidence interval, ITS: iontophoretic transdermal system, IV: intravenous, PCA: patient controlled analgesia.

Figure 4. Ability to mobilise at all time-points from 1 to 24 hours, mean score, intent-to-treat population. ITS: iontophoretic transdermal system, IV: intravenous, PCA: patient controlled analgesia.

Table 2. Primary and secondary outcome measures.

Measure	Fentanyl ITS: LS Mean (95% CI)	Morphine IV PCA: LS Mean (95% CI)	Difference (Fentanyl ITS – Morphine IV PCA) (95% CI)	p-value
<i>Secondary</i>				
Patient's pain rating (NRS)				
24 hours	1.97 (1.24, 2.70)	2.46 (1.51, 3.41)	-0.49 [-1.29, 0.30]	0.219 ^a
48 hours	0.39 [-0.47, 1.25]	0.92 [-0.10, 1.95]	-0.53 [-1.59, 0.53]	0.299 ^a
Study discharge	2.38 (1.38, 3.37)	1.67 (0.59, 2.76)	0.70 [-0.22, 1.63]	0.136 ^b
Nurse Ease-of-Care				
Total	0.28 (0.07, 0.49)	0.80 (0.55, 1.05)	-0.52 [-0.74, -0.30]	<0.001 ^a
Time-consuming subsection	0.31 (0.00, 0.62)	0.93 (0.56, 1.30)	-0.62 [-0.94, -0.29]	<0.001 ^a
Bothersome subsection	0.22 (0.02, 0.42)	0.71 (0.47, 0.95)	-0.49 [-0.69, -0.28]	<0.001 ^a
Satisfaction subsection	3.5 (3.07, 3.91)	3.5 (3.01, 4.01)	-0.02 [-0.45, 0.41]	0.922 ^a

CI: confidence interval; ITS: iontophoretic transdermal system; ITT: intent-to-treat; IV: intravenous; LS: least squares; NRS: Numerical Rating Scale; PCA: patient-controlled analgesia.

^ap-value was calculated from analysis of covariance, with centre, surgery type and treatment included as model terms in the analysis.

^bp-value was calculated from analysis of covariance, with centre, treatment and treatment duration included as covariates in the analysis.

patients (40.0%) received postoperative NSAIDs ($p = 0.163$). No patients in either treatment group received postoperative selective COX-2 inhibitors.

Patients in the fentanyl ITS treatment group stayed on study treatment longer than those in the morphine IV PCA group. The adjusted mean difference (fentanyl ITS minus morphine IV PCA) with 95% CI was 5.1 hours (1.8–8.4 hours), showing a statistically significant difference ($p = 0.003$) in patient duration on treatment for the two treatment groups. The adjusted mean difference (fentanyl ITS minus morphine IV PCA) with 95% CI was 4.7 hours (–2.0 to 11.3 hours) for the abdominal hysterectomy patients ($p = 0.159$), and the adjusted mean difference (fentanyl ITS minus

morphine IV PCA) with 95% CI was 5.4 hours (1.6–9.2 hours) for hip arthroplasty patients ($p = 0.006$).

Safety

There were 40 (69%) patients in the fentanyl ITS group and 38 (76%) patients in the morphine IV PCA group who experienced a TEAE (Table 3). Among all TEAEs reported, nausea and hypotension had the highest incidence rates (Table 3).

Seven patients (12.1%) in the fentanyl ITS group experienced treatment-emergent treatment-related application site AEs, five patients (8.6%) experienced application site erythema and two patients (3.4%)

Table 3. Treatment-emergent adverse events (TEAE) (safety population).

	Fentanyl ITS (N = 58), n (%)	Morphine IV PCA (N = 50), n (%)
Total number of patients with TEAEs	40 (69)	38 (76)
<i>TEAEs occurring in $\geq 5\%$ in either treatment group</i>		
Anaemia	4 (6.9)	2 (4.0)
Application site erythema	5 (8.6)	0
Bradycardia	4 (6.9)	5 (10.0)
Constipation	5 (8.6)	4 (8.0)
Dizziness	4 (6.9)	6 (12.0)
Dyspepsia	2 (3.4)	5 (10.0)
Haemoglobin decreased	4 (6.9)	4 (8.0)
Hypertension	3 (5.2)	1 (2.0)
Hypotension	14 (24.1)	13 (26.0)
Nausea	19 (33.0)	13 (26.0)
Pain	5 (8.6)	0
Pruritus	1 (1.7)	3 (6.0)
Pyrexia	5 (8.6)	4 (8.0)
Respiratory depression	1 (1.7)	3 (6.0)
Syncope vasovagal	3 (5.2)	1 (2.0)
Urinary retention	1 (1.7)	4 (8.0)
Vomiting	4 (6.9)	6 (12.0)
<i>Treatment-related TEAEs occurring in $\geq 5\%$ in either treatment group</i>		
Application site erythema	5 (8.6)	0
Constipation	2 (3.4)	3 (6.0)
Hypotension	3 (5.2)	6 (12.0)
Nausea	19 (33.0)	11 (22.0)
Pain	5 (8.6)	0
Pruritus	1 (1.7)	3 (6.0)
Respiratory depression	1 (1.7)	3 (6.0)
Vomiting	4 (6.8)	3 (6.0)

ITS: iontophoretic transdermal system; IV: intravenous; PCA: patient-controlled analgesia.

experienced application site vesicles. All application site AEs were mild in severity and resolved without medical intervention.

Both treatment groups experienced decreases in mean diastolic and systolic blood pressure (BP), increases in mean heart rate and slight decreases in respiratory rate.

Discussion

Overall, in this multicentre, randomised, open-label, active-controlled, parallel-group, prospective Phase IV study, patients in the fentanyl ITS group had significantly greater perceived ability to mobilise at all time-points up to 24 hours. This observation was consistent with results seen in previous Phase III fentanyl ITS studies.^{16–18} At 24 and 48 hours, the patients' adjusted mean pain ratings were also lower for fentanyl ITS patients. The time taken for a patient to mobilise is a key determinant of the patient's FFD from hospital. This target requires optimal postoperative pain control in order to afford the earliest and safest possible

mobilisation.^{2,25} Although there was not a statistically significant difference in FFD in our study, there was a statistically significant difference in mobilisation in favour of treatment with fentanyl ITS over morphine IV PCA. FFD is one of the secondary endpoints and the study was not powered for this endpoint. Further study is needed to determine whether the benefit of earlier mobilisation seen with fentanyl ITS confers a similar benefit in earlier FFD.

The mean scores for the Nurse EOC questionnaire showed that 'time-consuming' and 'bothersome' ratings were statistically significantly lower (better) for fentanyl ITS versus morphine IV PCA in this study. These results suggest that from a nursing perspective, fentanyl ITS is a more time-efficient and convenient postoperative pain control modality than morphine IV PCA. These findings are consistent with a previous report published by Lindley and colleagues who also found a statistically significant benefit with fentanyl ITS over morphine IV PCA in Nurse EOC.²⁶

A larger proportion of patients in the fentanyl ITS group required supplemental morphine within the

first 3 hours after the initiation of treatment, which was a statistically significant difference ($p = 0.029$). This, in part, may be due to the unblinded nature of this study and the fact that fentanyl was considered the investigational drug against the standard of care. It also could be due to the time to full uptake of fentanyl into the bloodstream with fentanyl ITS, and clinicians should be aware that supplemental pain medications may be needed with fentanyl ITS or IV PCA.

Overall, in this study, fentanyl ITS exhibited a similar safety profile with that of morphine IV PCA. However, in a pooled analysis of the active-comparator trials,^{15–18} fentanyl ITS was shown to have important safety advantages, especially in terms of opioid-related AEs, over morphine IV PCA. These included less hypotension, tachycardia, hypoventilation, pruritus and urinary retention observed with fentanyl ITS compared to morphine IV PCA.

A limitation of this study was that it was originally planned to include approximately 200 patients. However, following the early suspension and termination of the study, a total of 108 patients were randomised to study treatment. A second limitation is that the study was unblinded, with patients, investigators and other staff knowing the treatment. This could have introduced bias either way: (1) because the investigators and nursing staff were more familiar with and hence might favour IV PCA over fentanyl ITS, or (2) there may have been more interest in the innovative technique.

In summary, fentanyl ITS was effective and well tolerated in the management of acute moderate to severe postoperative pain. The study showed comparable efficacy between the two treatment modalities and demonstrated a broadly similar tolerability profile. The mobility and EOC ratings favoured fentanyl ITS, which may offer possible clinically significant and meaningful benefits to select patients in relation to factors affecting FFD, a proxy for accelerated recovery and reduced hospital residence times. This study provides the justification for further evaluation of the potential role for fentanyl ITS in enhanced post-surgical recovery programmes.

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