Patient-Controlled Transdermal Fentanyl Hydrochloride vs Intravenous Morphine Pump for Postoperative Pain

A Randomized Controlled Trial

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Context Patient-controlled analgesia (PCA) with morphine is commonly used to provide acute postoperative pain control after major surgery. The fentanyl hydrochloride patient-controlled transdermal system eliminates the need for venous access and complicated programming of pumps.

Objective To assess the efficacy and safety of an investigational patient-controlled iontophoretic transdermal system using fentanyl hydrochloride compared with a standard intravenous morphine patient-controlled pump.

Design, Setting, and Patients Prospective randomized controlled parallel-group trial conducted between September 2000 and March 2001 at 33 North American hospitals, enrolling 636 adult patients who had just undergone major surgery.

Interventions In surgical recovery rooms, patients were randomly assigned to intravenous morphine (1-mg bolus every 5 minutes; maximum of 10 mg/h) by a patient-controlled analgesia pump (n=320) or iontophoretic fentanyl hydrochloride (40-µg infusion over 10 minutes) by a patient-controlled transdermal system (n=316). Supplemental analgesia (morphine or fentanyl intravenous boluses) was administered as needed before and for the first 3 hours after activation of the PCA treatments. Patients then used the PCA treatments without additional analgesics for up to 72 hours.

Main Outcome Measures The primary efficacy variable was patient global assessment of the method of pain control during the first 24 hours. Additional efficacy measures were the proportion of patients discontinuing the study because of inadequate analgesia for any reason, patient-reported pain intensity scores on a 100-mm visual analog scale (VAS), and patient global assessments at 48 and 72 hours. Adverse effects were also recorded.

Results Ratings of good or excellent after 24 hours of treatment for the method of pain control were given by 73.7% of patients (233/316) who used transdermal fentanyl PCA and 76.9% of patients (246/320) who used intravenous morphine PCA; treatment difference was –3.2% (95% confidence interval, –9.9% to 3.5%; *P*=.36). Early patient discontinuations (25.9% fentanyl vs 25.0% morphine; *P*=.78) and last pain intensity scores (32.7 fentanyl vs 31.1 morphine on the VAS; *P*=.45) were not different between the 2 treatments. With continued treatment for up to 48 or 72 hours, more than 80% of patient assessments in each treatment group were good or excellent. The incidence of opioid-related adverse events was similar between the groups.

Conclusion An investigational PCA transdermal system using iontophoresis to deliver fentanyl provided postsurgical pain control equivalent to that of a standard intravenous morphine regimen delivered by a PCA pump.

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Patient-controlled analgesia (PCA) allows the patient to self-administer small doses of opioids, such as fentanyl, morphine, hydromorphone, or meperidine, as needed to manage pain. A key principle of PCA use is that it is initiated after titration to patient comfort with loading doses of intravenous (IV) opioids.[1] Thereafter, PCA is used to maintain a mild level of pain rather than total pain relief, allowing the patient to self-administer enough drug to achieve a comfortable balance between analgesia and adverse effects.[2-5] Existing PCA therapies infuse opioid analgesics through an IV line at a preset rate by electronic pumps or by disposable, fixed-volume devices when a patient activates a dosing button. Problems that compromise patient safety, such as programming errors, uncontrolled delivery of syringe contents, and patient tampering, have been reported.[6] Pump failures and syringe mix-ups are also possible.

To overcome these problems, a fentanyl hydrochloride patient-controlled transdermal system (PCTS) is under development as an alternative method that delivers small doses of fentanyl by iontophoresis with electro-

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transport delivery platform technology (E-TRANS; ALZA Corp, Mountain View, Calif). The system uses a low-intensity direct current to move fentanyl from a hydrogel reservoir into the skin, where it then diffuses into the local circulation and is transported to the central nervous system. The self-adhesive unit, about the size of a credit card, is worn on the patient's upper arm or chest, does not have the IV tubing, cables, and large pump of the IV PCA, and may facilitate patient mobility. The opioid analgesic fentanyl has a potential advantage over morphine in that it does not have active metabolites that can accumulate over time.[7]

For these advantages to be realized, the delivery method must provide pain control that is comparable to that of current standard therapy. The purpose of this study was to establish that the transdermal PCA delivery system is equivalent to a standard morphine IV PCA regimen in postoperative pain management.

METHODS

Study Design

A prospective, randomized, parallel-group, unblinded, active-controlled study was conducted from September 2000 to March 2001 at 29 US and 4 Canadian hospitals. Centers were recruited according to the knowledge of postoperative pain management of the local investigator and the proven ability of staff to conduct research. The institutional review board, research ethics board, or an independent centralized ethics review board approved the protocol. Patients provided signed informed consent during the screening process.

Randomization

A randomization schedule was created with computer-generated random numbers in a block size of 4 by using all patients, regardless of center. The patients were stratified by type of surgery (stratum 1: orthopedic, upper abdominal, and thoracic; stratum 2: all other procedures, including lower abdominal). Separate lists were generated for each stratum. The randomization was developed to eliminate any bias on the part of the investigators and their staff and to balance the number of patients between the 2 treatments and the surgery types. Eligible patients were assigned a study treatment (fentanyl PCTS or IV PCA morphine) with an interactive voice response system randomization procedure.[8] The investigators and their staff did not know the block size or the next treatment assignment before randomization.

Patient-Controlled Transdermal System

The fentanyl hydrochloride PCTS is manufactured to function within preset dosing specifications. It operates for 24 hours after the first dose is delivered or delivers a maximum of 80 doses and shuts off. The dose, controlled by the amount of electrical current, is fixed to not exceed 40 µg, the dosing interval is 10 minutes, and each dose is a 10-minute infusion. Drug delivery begins when the electrical current is activated by pressing the dosing button twice within 3 seconds. During delivery of the dose, the fentanyl PCTS cannot deliver additional doses, and delivery of the dose cannot be interrupted or extended.

The system provides an audible (beep) and visual indication (red light from a light-emitting diode) that a dose has begun. The light turns off momentarily when the dose has been completed and then flashes to indicate the approximate number of doses delivered. One flash represents delivery of 1 to 5 doses, 2 flashes represent delivery of 6 to 10 doses, and so on. Because the maximum number of doses allowed by the system is 80, the corresponding maximum number of flashes is 16. Alerts for nonfunctioning conditions are a short series of beeps (the fentanyl PCTS should be restarted) and continuous beeping (the system has shut down and should be removed). Thus, the audible and visual signals provide information on dosing similar to that of standard IV PCA.

The PCA pumps were programmed to deliver a 1-mg dose as a bolus, with a subsequent 5-minute lockout and a limit of 10 doses per hour (10 mg). The choice of the active comparator regimen is supported by the research of Owen and colleagues,[9] who showed an optimal balance between efficacy and adverse effects at an on-demand morphine dose of 1 mg compared with on-demand doses of 0.5 and 2 mg and using a dosing interval of 5 minutes. Ginsberg et al[10] demonstrated similar efficacy for PCA regimens incorporating various lockout periods from 2 to 8 minutes. Because of the confounding logistics—patients would have to press 2 dosing buttons simultaneously—the study was not blinded, which would have required an IV PCA pump and a fentanyl PCTS for each patient.

Patients

Names of prospective participants were selected from hospital surgical schedules. The patients were approached by anesthesiologists or surgeons to ascertain interest in joining the study. Patients (N=726) were screened within 2 weeks before enrollment, written informed consent was obtained, and medical history and a physical examination were conducted. Patients were instructed in the use of the fentanyl PCTS and IV PCA morphine pump and in the performance of the study assessments. Patients were aged at least 18 years; were American Society of Anesthesiologists physical status I, II, or III (no, mild to moderate, or severe systemic disturbance, respectively); were scheduled to undergo general or regional anesthesia for major abdominal, orthopedic, or thoracic surgery; and were expected to have moderate or severe pain requiring parenteral opioids for at least 24 hours after surgery.

Postoperative screening occurred when patients were admitted to the postanesthesia care unit (PACU; recovery room) after having undergone surgery. They were awake and breathing spontaneously, with a respiratory rate of 8/min to 24/min, arterial oxygen saturation by pulse oximetry (Sp_{O_2}) of at least 90% (with or without supplemen-

tal oxygen), able to answer questions and follow commands, and had been in the PACU for at least 30 minutes and were comfortable or had been brought to comfort with bolus IV doses of allowed opiates.

Patients (FIGURE 1) were excluded because they had received a long-lasting intraoperative regional analgesic or long-lasting intraspinal opioids, were expected to have postoperative analgesia supplied by a continuous regional technique, or were expected to require intensive care or would probably require additional surgical procedures within 36 hours. Postoperative patients were also excluded if they had received intraoperative or postoperative administration of opioids other than morphine, fentanyl, sufentanil, or alfentanil (except up to 50 mg of meperidine for shivering), were intubated at final screening assessments, were known or suspected to be opioid tolerant, had a recent history of opioid dependence, or had active systemic skin disease or active local skin disease that would preclude fentanyl PCTS application to their arms or chest. Pregnant women or patients with coexisting medical conditions likely to interfere with study procedures were not enrolled.

Study Protocol

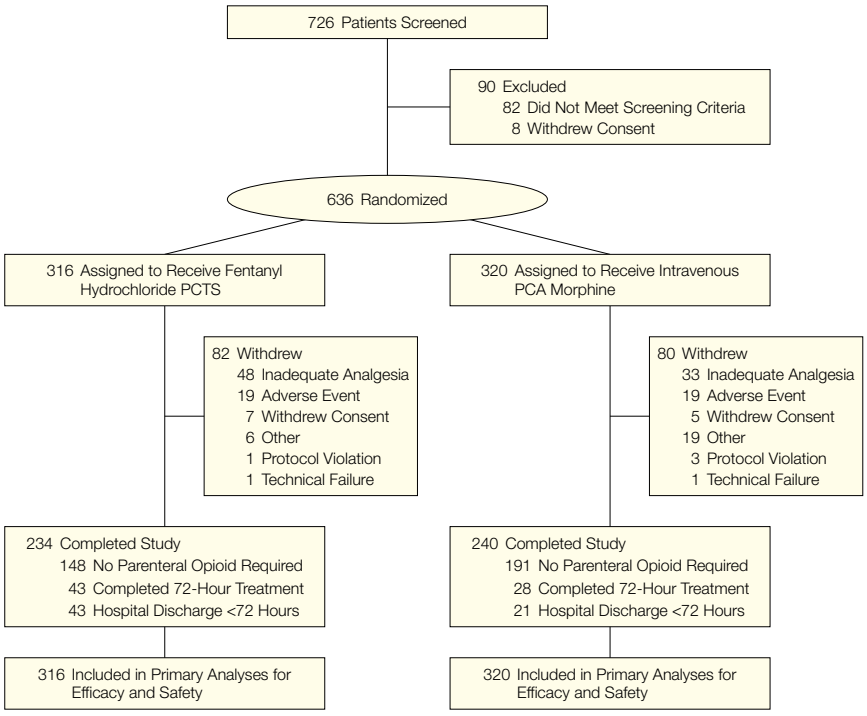
After surgery, patients were brought to the PACU and evaluated for the remainder of the study entry criteria (vital signs, general postsurgical condition). Patients were titrated to an acceptable level of comfort if needed with IV doses of morphine, fentanyl, sufentanil, or alfentanil. After patients had been in the PACU at least 30 minutes and were awake, alert, and comfortable, they marked their pain intensity on a 100-mm visual analog scale (VAS), and study staff recorded vital signs and Spo_2. These assessments completed the study entry criteria. Qualifying patients were then randomized in a 1 to 1 ratio to fentanyl PCTS or IV PCA morphine pump within each stratum as defined by surgery type.

Pain intensity, vital signs, and oxygen saturation were assessed again, and the time of this second set of assessments was the start of the treatment period, hour 0. Immediately, the fentanyl PCTS was applied or the IV PCA morphine pump was attached and enabled, and the patient was considered to be enrolled (n=636; Figure 1). The patient was again instructed about use of the PCA. Only the patient was to deliver a dose of fentanyl or morphine. Supplemental medication (single or multiple IV bolus doses of fentanyl [fentanyl PCTS group] or morphine [IV PCA morphine group]) was available on request during the first 3 hours after hour 0. Study measurements (vital signs, oximetry, number of doses delivered, pain intensity scores by VAS) were taken at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after enrollment and every 4 hours thereafter up to 72 hours. Sleeping patients were not awakened for pain assessments. Patient global assessments were obtained at 24, 48, and 72 hours or when the patient discontinued study medication, whichever came first. At any time in the study, patients who could not maintain pain relief at a comfortable level (with or without supplemental analgesia) were withdrawn from the trial to receive higher doses or additional analgesics to control their pain. Study staff monitored patients and recorded patient-reported adverse events, their severity and relationship to study treatments, concomitant medications, and assessments of erythema at the application site.

Outcome Measures

The patient global assessment at 24 hours was the primary efficacy end point. It consisted of a categorical evaluation (poor, fair, good, excellent) of the method of pain control. The patient was read aloud the following question by the investigator's staff, and the response was recorded: "Overall, would you rate this method of pain control during the last 24 hours as being poor, fair, good, or excellent?" Assessments were also collected at 48- and 72-hour points for patients who remained in the study. If the patient was withdrawn from the study

Figure 1. Flow of Patients Through the Trial



PCTS indicates patient-controlled transdermal system; PCA, patient-controlled analgesia.

before any 24-hour point, the assessment was completed at withdrawal, and this observation was carried forward to the next 24-hour point.

Pain intensity was measured on a 100-mm ungraded VAS that ranged from "no pain" (0 mm) to "worst possible pain" (100 mm). If the patient was withdrawn from the study before a 24-hour point, the pain-intensity measurement was completed at withdrawal. Patients were instructed to "Rate the pain you have at this time. On a scale of 'no pain' to 'worst possible pain,' rate where you feel your pain is at this moment." The patient was to make a vertical mark on a 100-mm ungraded horizontal line anchored by "no pain" and "worst possible pain" to indicate the amount of pain he or she was experiencing. If the patient was unable to make a mark, the investigator's staff marked the line as directed by the patient. The number of patients whose pain control was inadequate and who were withdrawn from the study was tabulated.

At specified times, the investigator's staff recorded the number of light flashes displayed by the fentanyl PCTS, the number of bolus doses delivered displayed on the IV PCA morphine pump, and the supplemental IV bolus doses of fentanyl or morphine used. The fentanyl PCTS dose was estimated by using 5 times the number of flashes minus 2.

Respiratory rate was the primary measure of systemic safety. Clinically relevant respiratory depression (CRRD) was defined as the simultaneous occurrence of bradypnea (respiratory rate less than 8/min sustained for 1 minute) and excessive sedation (the patient is not easily aroused). Clinically relevant respiratory depression was treated by ensuring a patent airway and providing supportive treatment to reestablish regular breathing (stimuli, IV naloxone). The patient could remain in study after 1 episode but would be withdrawn from study if 2 episodes occurred. Opioid analgesia was suspended until alertness and other vital signs were normal.

Statistical Analysis

Demographic and clinical variables were summarized according to treatment group for all randomized patients. Depending on the nature of the variable, either the 2-sample *t* test (numeric data) or χ^2 test (categorical data) was used to compare treatment groups.

Treated patients were those who received fentanyl PCTS or IV PCA morphine and completed a patient global assessment. For the efficacy analyses, patients who completed at least 72 hours of treatment, did not require further parenteral opioid analgesia, or were discharged from the hospital were considered to have completed the study. Patients who required parenteral opioid analgesia after 24 hours could continue in the study to a maximum of 72 hours of treatment.

The patient global assessment at 24 hours was the primary efficacy end point. The primary efficacy analysis was the construction of a 2-sided 95% confidence interval (CI) for the difference in success rate (proportion of excellent/good) according to the 24-hour patient global assessment data between the 2 treatment groups. The 2 treatments were considered therapeutically equivalent if the 95% CI of the difference in success rate fell within ±10% according to 2 one-sided tests with $\alpha = .025$ and a maximum acceptable difference of 10%.

All data from all centers and surgery types were pooled. Center was not used as a stratification variable because of the large number of centers required for patient enrollment. The mean of the last pain intensity score during the 24-hour treatment period(s) was analyzed with a 2-way analysis of variance model.

A sample size of 504 evaluable patients (252 patients in each treatment group) was planned for this study to provide an 80% probability to demonstrate the therapeutic equivalence in proportion between 2 treatments.

Table 1. Demographics of Treated Patients

Characteristics	Fentanyl PCTS (n = 316)	Intravenous PCA Morphine (n = 320)
Sex, No. (%)		
Female	229 (72.5)	238 (74.4)
Male	87 (27.5)	82 (25.6)
Age, y		
Mean (SD)	51.2 (15.3)	50.2 (14.8)
Range	18-90	18-86
Race, No. (%)		
White	233 (73.7)	234 (73.1)
Black	55 (17.4)	62 (19.4)
Hispanic	22 (7.0)	16 (5.0)
Asian	3 (0.9)	4 (1.3)
Other	3 (0.9)	4 (1.3)
Body mass index, mean (SD)*	29.1 (6.7)	29.3 (6.9)
Range	16.0-56.7	15.4-62.0
Surgical procedure, No. (%)		
Lower abdominal	176 (55.7)	185 (57.8)
Orthopedic bone	116 (36.7)	111 (34.7)
Upper abdominal	16 (5.1)	15 (4.7)
Thoracic/chest	6 (1.9)	4 (1.3)
Other	2 (0.6)	5 (1.6)

Abbreviations: PCA, patient-controlled analgesia; PCTS, patient-controlled transdermal system.
*Body mass index was measured as weight in kilograms divided by height in meters squared.

RESULTS

Of the 90 patients screened who did not enter the study, 82 did not meet the screening criteria and 8 met the screening criteria but decided not to enroll in the study (Figure 1). Demographic values were similar between the 2 treatment arms (TABLE 1). The patients were

predominantly female and white. The average age of the patients was about 50 years. Surgical procedures were primarily lower abdominal, with the majority represented by gynecologic surgery or orthopedic surgery (predominantly lower extremity and spinal procedures).

The 316 patients in the fentanyl PCTS group and the 320 patients in the IV PCA morphine group represent the patients in the intent-to-treat analyses for efficacy and safety (Figure 1). Of these treated patients, 82 (25.9%) withdrew early from fentanyl PCTS and 80 patients (25.0%) discontinued IV PCA morphine ($P=.78$; TABLE 2). Withdrawals because of inadequate analgesia were fewer but not statistically significant in the IV PCA morphine group (10.3%) compared with the fentanyl PCTS group (15.2%; $P=.07$).

In the withdrawal category of "other," a statistically significantly higher proportion of patients using IV PCA morphine (19 patients, 5.9%) discontinued for this reason than patients using fentanyl PCTS (6 patients, 1.9%) ($P=.009$). The most common "other" reason for withdrawal in both treatment groups was because the patient or investigator requested use of or a transfer to analgesic medications disallowed according to protocol (Table 2).

Efficacy

Fentanyl hydrochloride PCTS and IV PCA morphine were therapeutically equivalent according to the primary end point of global ratings of method of pain control during the first 24-hour treatment period. The distribution of patient ratings is displayed in TABLE 3; the overall distribution of the proportion of patients' ratings of poor, fair, good, or excellent between the 2 treatments is not statistically different ($P>.10$). The primary analysis was applied to a combined rating of good and excellent, which was reported by 73.7% of patients who received fentanyl PCTS and 76.9% of patients who received IV PCA morphine. The between-treatment difference in the good/excellent rating was –3.2% (95% CI, –9.9% to 3.5%; $P=.36$), which met the predefined statistical criterion for equivalence. With continued treatment for up to 48 or 72 hours, more than 80% of patient assessments in each treatment group were good or excellent.

The mean of the last recorded pain intensity scores (assessed on a VAS of 0-100) within the first 24 hours for all treated patients was also statistically indistinguishable between treatments, supporting the equivalence of fentanyl PCTS relative to IV PCA morphine (TABLE 4). These mean scores were 32.7 for the fentanyl PCTS group and 31.1 for the IV PCA morphine group ($P=.45$). The pain intensity scores were also comparable at all assessed times during the 24 hours (Table 4), and the distribution of pain scores between the treatment groups at 3 and 24 hours was similar (FIGURE 2). The

Table 2. Early Discontinuations of Treated Patients From the Study*

Reason for Discontinuation	No. (%) Fentanyl PCTS (n = 316)	No. (%) Intravenous PCA Morphine (n = 320)	*P* Value
All reasons	82 (25.9)	80 (25.0)	.78
Inadequate analgesia	48 (15.2)	33 (10.3)	.07
Adverse event	19 (6.0)	19 (5.9)	.97
Other†	6 (1.9)	19 (5.9)	.009
Patient/investigator requested or transferred to excluded pain medications	2	8	
Patient dissatisfaction with method of pain control	1	0	
Intravenous PCA line problems	0	5	
Study staff unavailable for additional 24-h treatment periods	1	1	
Did not require further parenteral analgesia	0	3	
Low oxygen saturation reading because of inaccurate oximeter	1	0	
Physician decision	0	1	
Overuse of PCA	0	1	
No fentanyl PCTS available	1	0	
Withdrew consent	7 (2.2)	5 (1.6)	.55
Suspected technical failure	1 (0.3)	1 (0.3)	>.99
Protocol violation	1 (0.3)	3 (0.9)	.32

Abbreviations: PCA, patient-controlled analgesia; PCTS, patient-controlled transdermal system.
*Only the primary termination reason was used for this analysis.
†"Other" reasons were analyzed as a single group.

Table 3. Patient Global Assessment of Pain Control Method*

Global Assessment of Method of Pain Control	No. (%) Fentanyl PCTS (n = 316)	No. (%) Intravenous PCA Morphine (n = 320)
Success	233 (73.7)	246 (76.9)
Excellent	122 (38.6)	108 (33.8)
Good	111 (35.1)	138 (43.1)
Failure	80 (25.3)	68 (21.3)
Fair	38 (12.0)	42 (13.1)
Poor	42 (13.3)	26 (8.1)
Data missing	3 (0.9)	6 (1.9)

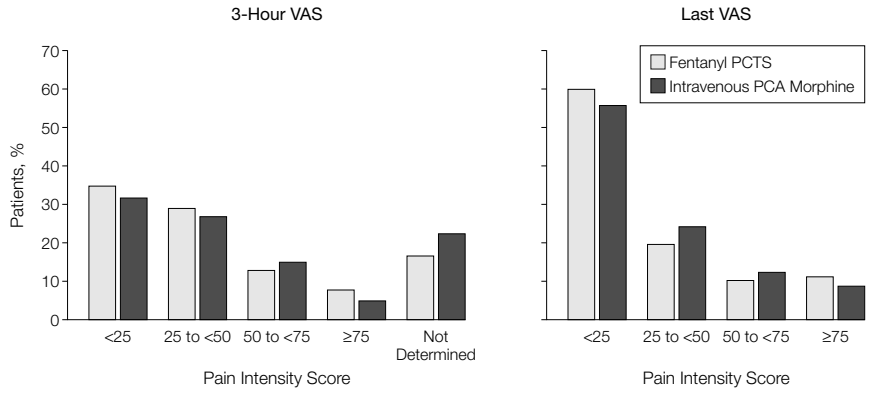
Abbreviations: PCA, patient-controlled analgesia; PCTS, patient-controlled transdermal system.
*At 24 hours or early discontinuation, patients were asked, "Overall, would you rate this method of pain control during the last 24 hours as being poor, fair, good, or excellent?" Data are reported for all treated patients. Overall distribution of ratings between treatments for patients was $P = .12$. Missing data were added to the poor/fair category for the computation of *P* values and confidence intervals. The between-treatment difference in the good/excellent ratings was –3.2% (95% confidence interval, –9.9% to 3.5%) ($P = .36$). *P* values were obtained using a χ^2 test.

Table 4. Pain Intensity Scores by Time During the First 24 Hours of Treatment*

	Fentanyl PCTS (n = 316)			Intravenous PCA Morphine (n = 320)		
Hours After Enrollment	No. of Patients in Study	No. (%) of Patients With VAS Data	VAS, Mean (SE)	No. of Patients in Study	No. (%) of Patients With VAS Data	VAS, Mean (SE)
0	316	314 (99.4)	43.3 (1.3)	320	317 (99.1)	44.5 (1.3)
0.5	316	269 (85.1)	41.7 (1.4)	320	264 (82.5)	43.1 (1.5)
1	316	262 (82.9)	40.4 (1.5)	320	254 (79.3)	40.8 (1.5)
2	314	272 (86.6)	38.2 (1.5)	320	260 (81.3)	38.5 (1.5)
3	311	264 (84.9)	34.9 (1.6)	317	249 (78.5)	34.5 (1.5)
4	303	252 (83.1)	33.5 (1.5)	315	253 (80.3)	33.3 (1.4)
6	291	256 (88.0)	33.8 (1.5)	309	270 (87.4)	31.6 (1.4)
8	288	227 (78.8)	31.2 (1.6)	304	223 (73.3)	30.8 (1.5)
12	280	213 (76.1)	30.0 (1.5)	300	215 (71.7)	29.1 (1.5)
16	276	214 (77.5)	29.3 (1.5)	297	241 (81.1)	30.6 (1.4)
20	271	244 (90.0)	27.5 (1.4)	289	264 (91.3)	29.4 (1.3)
24	260	252 (96.9)	24.3 (1.3)	270	253 (93.7)	27.3 (1.4)
Last recorded score†	316		32.7 (1.6)	320		31.1 (1.5)

Abbreviations: PCA, patient-controlled analgesia; PCTS, patient-controlled transdermal system; VAS, visual analog scale.
*Pain intensity was marked on a VAS from 0 (no pain) to 100 (worst pain imaginable). Only patients with a recorded score at the time point were included in the calculation of the mean (patients were not awakened to obtain a pain score and such data were considered missing).
†The last recorded score occurred at 24 hours or at early discontinuation of the treatment within the first 24 hours. $P = .45$ for the difference between the averages of the last pain assessment, based on analysis of variance.

Figure 2. Distribution of Pain Intensity Scores at 3 Hours and Last Score



Pain intensity scores measured on a 100-mm visual analog scale (VAS) with 0=no pain to 100=worst imaginable pain. Distribution of pain scores was similar between the 2 treatment groups after 3 hours and at the last pain measurement recorded. PCTS indicates patient-controlled transdermal system; PCA, patient-controlled analgesia.

magnitude of these scores reflected a level to which patients commonly titrate themselves with opioid PCA.[3-5]

Fentanyl hydrochloride PCTS dosing was qualitatively similar to IV PCA morphine pump (TABLE 5). Patients in both treatment groups administered more doses per hour during the first 6 hours than in the subsequent 66 hours. The amount of fentanyl (1244 µg) and morphine (43.9 mg) was typical of reported opioid consumption during the first 24 hours after major surgery.[11] The percentage of the maximum possible doses used during the entire 72-hour study period was 22.0% for fentanyl PCTS and 17.2% for IV PCA morphine treatments. Supplemental IV opioid was allowed during the first 3 hours after treatment initiation to retitrate patients to comfort. Both groups were similar in that their pain during the first 3 hours after treatment initiation required administration of supplemental analgesic to establish comfort. The proportion of patients who received supplemental IV opioid was similar for both treatment groups (Table 5).

Safety

The incidence of opioid-related adverse events was similar between the fentanyl PCTS and IV PCA morphine groups (TABLE 6). Other opioid-related adverse events that occurred less frequently in the PCTS group and IV PCA group were hypotension (1.3%, 1.9%, respectively), urinary retention (1.6%, 0.6%), hypoventilation (0.3%, 1.3%), and ileus (0.9%, 0.6%). Adverse events, most of which were considered treatment-related, led to early discontinuations for 6% of patients per treatment group (Table 2). Two of 29 serious adverse events reported for 21 patients were considered to be related to study medication: a report of severe confusion that prolonged hospitalization was attributed to fentanyl PCTS treatment, and a report of CRRD was attributed to IV PCA morphine treatment. The CRRD was reported as a respiratory adverse event (4/min, moderate sedation). The patient was given naloxone and was withdrawn from the study. No patient who received fentanyl PCTS developed CRRD.

Application site reactions (6.3%) reported as spontaneous adverse events

by fentanyl PCTS patients were mild to moderately severe in all but 1 case. Scheduled skin evaluations at 24 hours after system removal revealed erythema in approximately half (53.8%) of the fentanyl PCTS patients. Most of this erythema was mild, resembling sunburn or tanning marks. None required treatment, and all resolved within 4 weeks.

COMMENT

The fentanyl hydrochloride PCTS provided PCA after major surgery that was therapeutically equivalent to a standard IV PCA morphine regimen, as judged by patient global assessments, the predefined primary end point. The other efficacy variables—pain intensity scores and discontinuation for inadequate analgesia—confirmed the primary efficacy variable. Within the subset of patients who withdrew for inadequate analgesia, more patients were in the fentanyl PCTS group (15.2%) compared with the IV PCA group (10.3%; Table 2). However, pain intensity scores of the 2 treatments were comparable at each assessment (Table 4), and the dosing pattern of the 2 treatments with respect to frequency of dosing over time and the proportion of total available doses activated was similar (Table 5). These data do not reveal a reason for the different withdrawal rate. Eight patients in the IV PCA group withdrew from the study to use study-prohibited analgesics compared with 2 in the fentanyl PCTS group (Table 2). It is possible that these patients should have been attributed to withdrawal for inadequate analgesia.

Individualized dosing with PCA addresses the subjective nature of a patient's ability to tolerate pain and his or her requirement for and response to opioids. PCA is initiated when patients have been made comfortable. For postoperative patients, this initiation generally occurs after administration of loading doses of IV opioids,[7] which results in large interpatient variation (up to 5-fold) in plasma concentrations associated with analgesic efficacy.[7] Therefore, PCA delivery systems are ideally suited to provide safe and effective individualized treatment of acute pain, allowing self-titration in small-dose increments to maintain comfort.

The safety and efficacy of PCA with systemic opioids in the postoperative setting in general and with fentanyl specifically have been widely reported for nearly 20 years, at doses ranging from 10 to 60 µg and lockout intervals ranging from 1 to 10 minutes.[1,3-5,10,12-14] Fentanyl is considered to have 50 to 100 times the potency of morphine according to responses to IV bolus doses.[15] With this conversion factor, the average amount of fentanyl accessed by patients in the first 24 hours of this study (1244 µg) would be equivalent to 62 to 124 mg morphine, which exceeds the amount of morphine (43.9 mg) accessed by IV PCA patients (Table 5). This discontinuity may be because the number of fentanyl doses delivered is estimated within a 1- to 5-dose range by observing the number of dosing flashes from the fentanyl PCTS, and the pharmacodynamic actions of a 10-minute infusion of 40 µg of fentanyl may be different than an IV bolus of 40 µg of fentanyl.[7] The 40-µg dose for the PCTS was selected after the study by Camu et al[14] in which a 10-minute infusion of 40 µg yielded an optimal profile of pain relief and safety compared with infusions of 20 or 60 µg of fentanyl.

Table 5. Doses Used and Patients Requiring Supplemental Analgesia in the First 24 Hours*

Measure	Fentanyl PCTS (n = 316)	Intravenous PCA Morphine (n = 320)
Analgesic doses used in the first 24 hours, No.*		
Mean (SD)	33.4 (19.7)	45.9 (26.9)
Range	3-93†	0-129
No. of doses available/24 h	144	240
No. of doses/patient/h		
Mean	1.39	1.91
No. of doses available	6	10
Total opioid use in 24 h, mean (SD)	1244 (785.6) µg‡	43.9 (26.6) mg
Supplemental IV opioid in the first 3 h		
Patients requiring supplemental IV opioid, No. (%)§	72 (22.8)	87 (27.2)
Total doses, No.	215	224

Abbreviations: PCA, patient-controlled analgesia; PCTS, patient-controlled transdermal system; IV, intravenous.
*The total number of PCTS doses was estimated as 5 × the number of displayed flashes − 2. The total number of PCA morphine doses was read directly from the pump.
†Range of fentanyl >80 indicates use of 2 systems in 24 hours.
‡This amount equals 62-124 morphine equivalents based on fentanyl having a potency 50-100 times that of morphine.[19]
§$P = .20$ by χ^2 test.

Table 6. Treatment-Related Adverse Events*

Adverse Event	No. (%)	
	Fentanyl PCTS (n = 316)	Intravenous PCA Morphine (n = 320)
Nausea	129 (40.8)	147 (45.9)
Headache	36 (11.4)	24 (7.5)
Vomiting	31 (9.8)	27 (8.4)
Pruritus	26 (8.2)	40 (12.5)
Application site reactions (erythema, itching, vesicles, other)	20 (6.3)	0
Constipation	12 (3.8)	7 (2.2)
Hypoxia	12 (3.8)	7 (2.2)
Fever	11 (3.5)	13 (4.1)
Dizziness	6 (1.9)	12 (3.8)
Somnolence	6 (1.9)	7 (2.2)
Anxiety	4 (1.3)	9 (2.8)

Abbreviations: PCA, patient-controlled analgesia; PCTS, patient-controlled transdermal system.
*Reported at a frequency of at least 2%. A patient may be reported in more than 1 category.

The inherent safety of PCA is that the dosing frequency is controlled as needed by the patient for pain relief, reducing the possibility of overdose as pain requirements are met. A meta-analysis of 15 randomized controlled studies showed that postoperative patients using PCA obtained significantly better pain relief than those using intramuscular analgesia, with no increase in adverse effects.[16] The study also showed that patients using PCA in this setting tended to use less total opioid and had shorter hospital stays, although this trend was not statistically significant. The Acute Pain Management Panel, in its *Clinical Practice Guideline* for acute pain management,[17] also notes that for patients who have had thoracic surgery, PCA results in incrementally improved analgesia, increased patient satisfaction, and trends toward improved pulmonary function and earlier recovery or discharge compared with intramuscular or bolus IV injections.

Building on the PCA concept that has become the standard of care in many facilities for the management of postoperative and other acute pain, fentanyl PCTS was designed to provide a preprogrammed, self-contained, noninvasive alternative to IV PCA. Key system design characteristics, the choice of the 40-µg dose on demand, the 10-minute dosing interval, and the 80-dose maximum available from each system, were carefully selected according to the substantial literature in this field and corroborated in phase 1 and 2 clinical trials.[12,14] The fentanyl PCTS does not incorporate a continuous infusion with the on-demand bolus doses because previous studies indicate that a continuous basal infusion does not enhance efficacy during acute use.[6,7] This integrated drug-device delivery system incorporates design features that effectively prevent unintentional dosing during use, such as a recessed dosing button, double-push activation, and electronic lockout and disablement features.

Limitations of this study are the open design and lack of placebo control. The study was not blinded, because patients would have been required to push the buttons of the pump and transdermal PCA system simultaneously when seeking pain medication and would shortly have determined which delivery system contained opioid. Randomized, blinded, placebo-controlled trials have been conducted that demonstrate the superiority of the fentanyl PCTS for pain control compared with a PCTS that did not deliver fentanyl.[18]

Another limitation is that no single morphine IV PCA regimen is "approved" for postoperative analgesia, and the morphine IV PCA regimen chosen for this study was a fixed dose, whereas physicians tend to think of IV PCA as adjustable. Although current IV PCA pumps allow a wide variety of dosing regimens, the preferred doses reported in the literature are similar.[6] In practice, clinicians seldom deviate from a narrow dose range similar to those used in this study. Patients with extreme opioid requirements may require a customized regimen, but this is the exception. For example, fentanyl PCTS may not be appropriate for opioid-tolerant patients whose opioid dose requirement may be higher than that provided by the system. The fentanyl PCTS may also be criticized for lack of programming flexibility, but this feature would introduce the risk of programming errors and dosing mistakes.[6] In addition, current approaches for acute pain management use adjuvant analgesics such as regional blocks, wound infiltration, or systemic nonsteroidal anti-inflammatory drugs with PCA.[19] Future fentanyl PCTS studies will need to address its use in a multimodal analgesic setting.

An investigational PCA transdermal system using iontophoresis to deliver fentanyl provided postsurgical pain control equivalent to that of standard IV morphine delivered by a PCA pump. The PCTS offers the advantages of needle-free, preprogrammed operation in a small, self-contained unit.

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data. All authors contributed to the writing and review process and approved the final manuscript. To ensure accuracy and avoid any potential bias, a statistician (Brad Efron, PhD) who was not part of the study and who is not employed by ALZA had access to all of the data and performed an independent review. Dr Atkinson was responsible for the design and conduct of the trial and Dr Khanna was responsible for the design, data management, and statistical analysis of the trial. Both authors are employees of the company. Drs Chung, Reynolds, and Viscusi do not have financial interests in ALZA or own stock in Johnson & Johnson, the parent corporation.

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In the degree in which I have been privileged to know the intimate secrets of hearts, I ever more realize how great a part is played in the lives of men and women by some little concealed germ of abnormality. For the most part they are occupied in the task of stifling and crushing those germs, treating them like weeds in their gardens. There is another and better way, even though more difficult and more perilous. Instead of trying to suppress the weeds that can never be killed, they may be cultivated into useful or beautiful flowers. For it is impossible to conceive any impulse in a human heart which cannot be transformed into Truth or into Beauty and into Love.

—Havelock Ellis (1859-1939)