Evaluation of Morphine Versus Fentanyl for Postoperative Analgesia After Ambulatory Surgical Procedures

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Adequate postoperative analgesia without side effects is necessary to facilitate same-day discharge of ambulatory patients after ambulatory surgery. This study compared the use of intravenous morphine and fentanyl after painful ambulatory procedures with respect to analgesic efficacy, the incidence of side effects, and impact on the patient's readiness for discharge. Fifty-eight patients undergoing ambulatory surgery were prospectively randomized to receive morphine or fentanyl for postoperative analgesia and studied in double-blind fashion. The drugs were administered in equipotent doses in the postanesthesia care unit (PACU) and were titrated against pain scores until a visual analog score <40 mm was achieved and the patient was satisfied with the level of analgesia. In the ambulatory surgical unit, oral analgesia was available. Pain scores, amount of analgesia used, the incidence of side-effects (nausea and vomiting, sedation and dizziness), the times to achieve recovery milestones, and fitness for discharge were studied. Equal amounts of morphine and fentanyl were used in the PACU, but pain scores were higher in the fentanyl group in the ambulatory surgical unit. In addition, the fentanyl group required more oral analgesia than the morphine group (69% vs 17%; $P < 0.0002$). The incidence of in-hospital side effects was similar. However, the morphine group had a more frequent incidence of postdischarge nausea and vomiting than the fentanyl group (59% vs 24%; $P < 0.016$). There was no significant difference in the duration of stay in the PACU (morphine vs fentanyl, 69 ± 15 min vs 71 ± 20 min), the times to achieve recovery milestones, and fitness for discharge (morphine vs fentanyl, 136 ± 41 min vs 132 ± 40 min). The short duration of fentanyl was not associated with faster discharge times; most patients required additional analgesia to control pain. Morphine produced a better quality of analgesia but was associated with an increased incidence of nausea and vomiting, the majority of which occurred after discharge.

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After ambulatory surgery, persistent, intractable pain is one of the most common surgical complications (1). Adequate analgesia is necessary to facilitate same-day discharge of ambulatory patients whereas inadequate analgesia may delay or prevent discharge. Recently, the range of procedures undertaken on an ambulatory basis has increased. More complex and painful procedures are being performed, which means the choice of analgesia is of greater significance in facilitating discharge.

Pain in the immediate postoperative period often requires opiates. Alternatives, such as nonsteroidal antiinflammatory drugs or local anesthetic techniques, may be used, but these are not always possible for every patient or procedure. Opiates will therefore continue to be an important part of the armamentarium available to provide rapid control of severe postoperative pain. However, opiates have side effects, specifically nausea, sedation, and dizziness, which may delay the fitness of patients for discharge (2).

Morphine and fentanyl are widely used in ambulatory patients to provide analgesia during Phase I recovery in the postanesthesia care unit (PACU). As fentanyl has a faster onset time, its use may provide more rapid control of pain (3) and avoid unnecessary extra does which may be administered when a drug of slower onset is used in small incremental doses titrated to pain. This may allow a reduction of the total dose of opioid used and reduce the incidence of dose-dependent opiate-related side effects. The reduced side effects in combination with a short duration of action of fentanyl may facilitate earlier discharge and produce fewer complications after discharge.

Despite the theoretical advantages of fentanyl in the early management of postoperative pain, no study has examined the effectiveness of equipotent doses of morphine and fentanyl when administered in the

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early postoperative period in ambulatory surgical patients. This study compares the use of intravenous (IV) morphine and fentanyl after painful ambulatory procedures with respect to analgesic efficacy, the incidence of side effects, and impact on the patient's readiness for discharge. We hypothesize that the use of fentanyl will result in fewer side effects and a quicker discharge after ambulatory surgery.

Methods

With approval from the institutional human ethical research committee, written informed consent was obtained from ASA physical status I and II patients between 18 and 65 yr of age. These study patients were scheduled to undergo ambulatory procedures that were anticipated to be painful and to require postoperative opiate analgesia. The operations chosen, orthopedic operations including operative arthroscopic surgery, the removal of hardware, and breast augmentation, were based on data previously collected at our ambulatory surgical unit (4). Patients with a history of adverse reactions to opiates, a history of postoperative nausea and vomiting, or chronic pain were excluded from the study.

Patients were assigned by a table of random numbers to receive either morphine or fentanyl IV for postoperative analgesia during their PACU (Phase I) stay. The study used a prospective, randomized double-blind design in which neither the anesthesiologist, the nurse, the physician observer, nor the patient knew the type of postoperative IV analgesic given.

A standardized general anesthetic was administered. No premedication was given. After a small defasciculating dose of vecuronium, anesthesia was induced with propofol 2–2.5 mg/kg and fentanyl 1.5 μg/kg IV. Intubation was facilitated with 1.5 mg/kg succinylcholine. The lungs were mechanically ventilated and anesthesia was maintained with nitrous oxide:oxygen (70%:30%) and end-tidal isoflurane 0.5%–1% in a semiclosed circle system using intermittent positive pressure ventilation. Vecuronium was used to maintain muscle relaxation. Patients manifesting signs of inadequate analgesia received supplemental fentanyl in doses of 25–50 μg at the discretion of the anesthesiologist. Criteria for supplemental administration of fentanyl included heart rate and/or mean arterial pressure exceeding 20% of baseline values, sweating, or lacrimation. At the end of the procedure, residual muscle relaxation was reversed using neostigmine 0.04 mg/kg and glycopyrrolate 0.06 mg/kg. No prophylactic perioperative antiemetic was used.

Routine PACU care was provided. Management included the administration of oxygen 40% by face mask, and the recording of vital signs and Aldrete scores (5). All assessments of patients were done by an independent physician-observer blinded to the analgesic treatment group.

In the PACU (Phase I), pain scores were measured initially every 5 min using a 100-mm visual analog scale (VAS); 0 mm represented no pain and 100 mm represented the worst imaginable pain. IV analgesia was given and titrated to the pain score recorded every 5 min. The drugs were used in equipotent analgesic doses administered from syringes of similar appearance prepared by the pharmacy (6). Each syringe contained 10 mL of either 1 mg/mL morphine or 12.5 μg/mL fentanyl and was administered by volume as 1 or 2 mL IV boluses (12.5–25 μg fentanyl or 1–2 mg morphine) according to the following regimen: VAS ≥60 mm, 2 mL; VAS <60 mm and ≥40 mm, 1 mL; VAS <40 mm, nil or on specific request by the patient. The maximum dose permissible in the study was 20 mL (20 mg morphine or 250 μg fentanyl). Repeated boluses of either morphine or fentanyl were given every 5 min until the VAS pain score was <40 mm. Fentanyl 12.5–25 μg boluses every 5 min was chosen based on the regimen suggested by Wetchler (7). The larger dose gave flexibility and facilitated the control of more severe pain. Once a VAS pain score of <40 mm was achieved and the patient was satisfied with the level of analgesia (did not accept further analgesia when it was offered and pain scores were <40 mm), pain scores were measured every 10 min. Patients were discharged from the PACU when the Aldrete score was 10 and 20 min after the last IV analgesia injection.

In the ambulatory surgical unit (Phase II) pain was treated by oral analgesic (acetaminophen 300 mg and codeine 30 mg) at the request of the patient. Pain scores were measured on arrival and every 15 min until discharge criteria were satisfied. Patients were discharged with a supply of the same oral analgesic.

Nausea was recorded using a 100-mm VAS (0 mm representing no nausea and 100 mm representing severe nausea/likely to vomit) every 15 min during the hospital stay. Episodes of retching and vomiting were also recorded. Persistent nausea lasting longer than 5 min, retching, or vomiting was treated with IV ondansetron 4 mg. Ondansetron was chosen due to its lower incidence of sedation (8).

Sedation was recorded using a 100-mm VAS (0 mm representing fully awake and 100 mm representing very drowsy, could fall asleep) every 15 min during both Phases I and II. Dizziness was also recorded at the same times using a VAS (0 mm representing no dizziness and 100 mm representing severe dizziness). The patients were also asked directly about dizziness upon transfer and mobilization.

During Phase II, the need for oral analgesic and the time to sit, eat, drink, mobilize, void, and achieve fitness for discharge defined by a postanesthetic discharge scoring system (PADSS) ≥9 were evaluated by the same independent physician observer (9). The PADSS is based on five criteria: 1) vital signs, i.e., blood pressure, heart rate, temperature, and respiratory rate; 2) ambulation; 3) pain/nausea; 4) surgical bleeding; and 5) oral input/urinary output. Each of the main criteria is graded from 0 to 2 and a summated score of 9 to 10 indicates that the patient is fit for discharge. The PADSS was used as a consistent, objective end point in as much as most delays in achieving satisfactory home readiness scores may be due to nonmedical reasons (1).

A standardized telephone interview was conducted at 24 h by the same physician observer to assess problems after discharge. Patients were asked to rate the overall intensity of pain experienced after leaving the hospital (none, mild, moderate, or severe), the amount of analgesic used, whether they had experienced drowsiness, dizziness, and nausea, and if they had actually vomited. Satisfaction with analgesia provided in the PACU (Phase I) was assessed by asking whether they would be happy to have the same analgesia again.

Chung et al. (10) suggested 130 ± 38 min to be the mean ± SD to achieve a PADSS ≥9 when morphine was used for PACU analgesia in our institution. Assuming a reduction of 30 min would be clinically worth detecting, a total sample size of 60 was calculated based on a β value of 0.2 and an α value of 0.05. Parametric data were analyzed with the unpaired Student *t*-test including pain scores. Within group differences in pain scores were analyzed using repeated-measures of analysis of variance. Multiple comparisons of pain scores to the initial pain score were made with Dunnett's test. Nonparametric data were analyzed using the χ^2 test with the Yates continuity correction. A P value <0.05 was considered statistically significant. All results are expressed as mean ± SD.

Results

Sixty ambulatory patients of ASA physical status I or II between the ages of 18 and 65 yr were enrolled in the study. Two patients were withdrawn from the study; one in the fentanyl group who was admitted to the hospital because of inadequate pain control and was given morphine for analgesia, and one in the morphine group who developed weals and itchiness at the site of the injection after the first administration. Thus, data from 58 patients were analyzed.

The two groups were similar with respect to demographics, duration of anesthesia, and the amount of intraoperative fentanyl and propofol given (Table 1).

Table 1. Patient Demographics and Surgery

	Morphine (n = 29)	Fentanyl (n = 29)
Age (yr)	34 ± 10	37 ± 11
Sex (M:F)	15:14	21:8
Weight (kg)	76 ± 18	80 ± 14
Anesthetic duration (min)	56 ± 16	64 ± 21
Propofol (mg)	193 ± 54	208 ± 40
Intraoperative fentanyl (μg)	126 ± 25	132 ± 30
Operation		
Arthroscopy	22	23
Shoulder	14	19
Elbow, knee, or ankle	8	4
Hardware removal	5	4
Breast augmentation	2	2

Values are mean ± SD.

On arrival in the PACU, both groups had similar VAS pain scores (morphine versus fentanyl, 57 mm versus 61 mm) (Figure 1). At 10, 20, 30, and 40 min postoperatively, there was no significant difference in VAS pain scores between groups. During the stay in the PACU, both groups used similar amounts of equipotent doses of opiates: morphine 8.0 ± 4 mL (8 ± 4 mg) and fentanyl 8.0 ± 4 mL (100 ± 50 μg). The cumulative doses of analgesia used at 10, 20, 30, 40, 50, and 60 min postoperatively were similar in both groups (Figure 2).

After 20 min in the PACU, both groups had achieved significant reductions in VAS pain scores compared to their baseline values on arrival (Figure 1). In the morphine group the pain reduction was sustained throughout the recovery period. The fentanyl group had higher pain scores at 30 min than at 20 min (Figure 1). At 30 min, the pain score in the fentanyl group was no longer significantly reduced compared with the arrival pain score.

The morphine group had significantly lower VAS pain scores on arrival in the ambulatory surgical unit (Phase II), after 30 min in Phase II, and at the time of achieving PADSS ≥9, $P < 0.05$ (Figure 1). Significantly fewer patients required supplemental oral analgesia in the ambulatory surgical unit in the morphine group versus the fentanyl group: 5 of 29 (17%) vs 20 of 29 (69%); $P < 0.0002$.

The incidence of nausea and vomiting was not significantly different between the morphine and the fentanyl groups during Phase I and Phase II recovery (Table 2). The incidence of nausea and vomiting was significantly higher in the morphine group after discharge from the hospital. The total number of patients experiencing nausea and vomiting either in the hospital or after discharge was also significantly greater in the morphine group. Sedation scores were similar for both groups in Phase I and on arrival in Phase II (Table 2). The incidence of dizziness was low, and

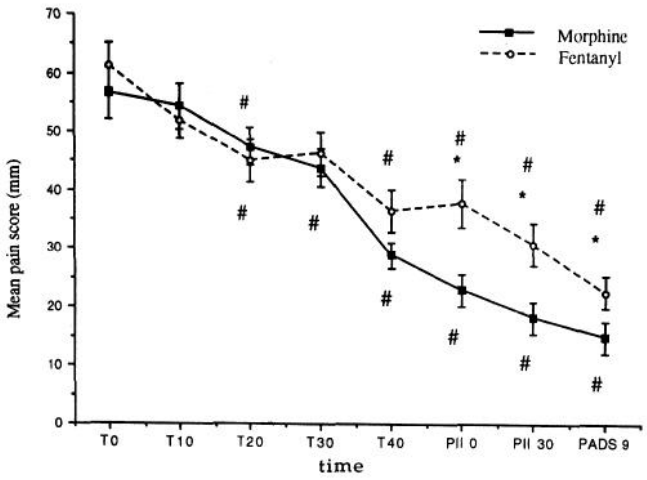

Figure 1. Visual analog scale (VAS) pain scores for morphine (n = 29) and fentanyl (n = 29) groups at different time intervals postoperatively. T0 = arrival in postanesthesia care unit (PACU). T10, T20, T30, and T40 = 10, 20, 30, and 40 min in the PACU. PII 0 = time of arrival in Phase II. PII 30 = 30 min in Phase II and PADS 9 = time of postanesthesia discharge score ≥9. * Between group differences in VAS pain scores at the times indicated, $P < 0.05$; ¶ within groups VAS pain scores for both morphine and fentanyl significantly different from baseline VAS pain scores at T0, $P < 0.05$.

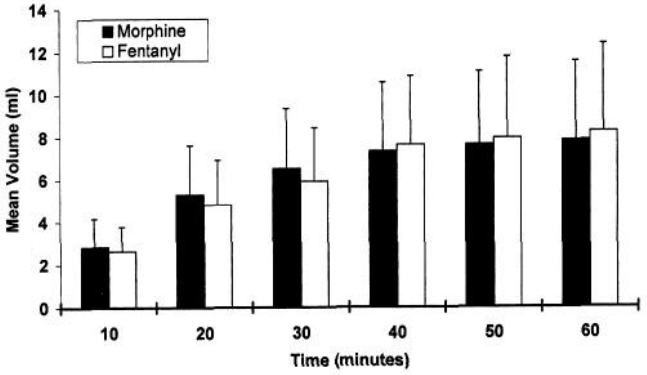

Figure 2. Cumulative doses of morphine and fentanyl (mean ± SD) administered at 10, 20, 30, 40, 50, and 60 min postoperatively.

when it occurred, it was mild and of a transient nature. Eleven patients in the morphine group and nine in the fentanyl group experienced dizziness in the hospital (not significant).

The times to drink, sit, eat, mobilize, and void were similar in both the morphine and fentanyl groups (Figure 3). There was no significant difference in the duration of stay in the PACU (morphine versus fentanyl, 69 ± 15 min versus 71 ± 20 min) and the time to reach a PADSS score ≥9 (morphine versus fentanyl, 136 ± 41 min versus 132 ± 40 min).

In the 24 h after discharge, there were no differences in the overall pain experienced or in the incidence of dizziness or drowsiness (Table 2). In each group, a similar number of patients indicated that they were satisfied to receive the same analgesia for pain in the PACU if the operative procedure was repeated.

Table 2. Side Effects: Nausea and Vomiting/Sedation/24-h Interview

	Morphine (n = 29)	Fentanyl (n = 29)
Nausea and vomiting, n (%)		
In hospital (Phase I and Phase II)	10 (34)	5 (17)
After discharge	17 (59)*	7 (24)
In hospital and after discharge	23 (79)†	11 (38)
Antiemetic	7 (24)	4 (14)
Sedation scores, mean ± SD		
Arrival PACU	67 ± 22	63 ± 24
30 min in PACU	32 ± 22	34 ± 23
Arrival ASU	13 ± 20	14 ± 16
24-h interview		
Pain		
Mild	4	5
Moderate	22	15
Severe	3	9
Tablets used	4 ± 3	4 ± 3
Other symptoms		
Drowsiness	7	6
Dizziness	6	4
Satisfaction	22	21

For the in hospital and after discharge nausea and vomiting evaluations, patients are only included once.
PACU = postanesthesia care unit; ASU = ambulatory surgical unit.
* $P < 0.016$; † $P < 0.003$.

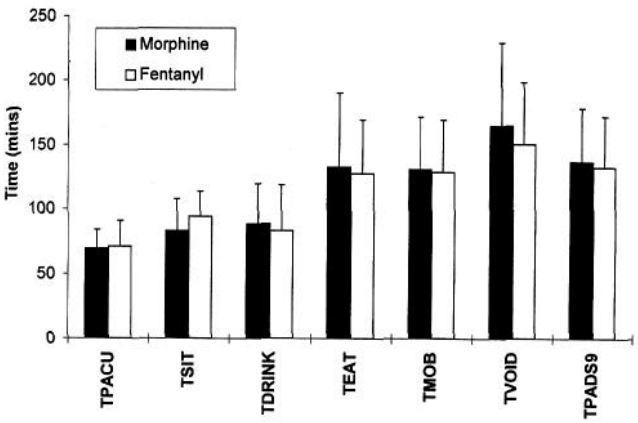

Figure 3. Time of recovery milestones (mean ± SD) for patients receiving morphine (n = 29) or fentanyl (n = 29). TPACU = time spent in the postanesthesia care unit (Phase I); TSIT = time to sit; TDRINK = time to drink; TEAT = time to eat; TMOB = time to mobilize; TVOID = time to void; TPADS9 = time to achieve postanesthesia discharge score ≥9, when patient is fit to be discharged from ambulatory surgical unit.

Discussion

This study has shown morphine and fentanyl to be comparable in treating postoperative pain in Phase I recovery after painful ambulatory procedures. Morphine produced sustained analgesia, whereas patients receiving fentanyl required additional oral analgesia

during Phase II before discharge criteria were achieved. There were no differences in the times to achieve fitness for discharge, but the morphine group had a significantly higher incidence of nausea and vomiting after discharge.

The sustained action of morphine appeared to have advantages with respect to the control of pain throughout the recovery period. Ambulatory patients are transferred from Phase I to Phase II and then encouraged to mobilize, which may exacerbate pain. If pain occurred, it might discourage the achievement of recovery milestones. The persistence of pain and the need for further analgesia contributed to the fentanyl group not achieving discharge criteria any faster than the morphine group. In this study, oral analgesics were given in Phase II at the request of the patient. If fentanyl is used after procedures that are associated with persistent postoperative pain, the early use of oral analgesia to coincide with its offset and produce sustained analgesia throughout the perioperative period may then facilitate earlier discharge, avoiding the delays associated with inadequate pain relief.

Although we demonstrated the prolonged analgesic action of morphine, we did not find any differences in dizziness and sedation which might have delayed recovery in the morphine group. Although clinical studies have failed to demonstrate significant differences in the ability of different opiates to produce emesis, a study in dogs suggested that IV morphine caused gastric relaxation and more nausea and vomiting than equipotent doses of fentanyl (11). In our study, morphine was associated with a higher incidence of nausea. Most occurred after discharge. Thus there were no delays in achieving discharge criteria in the morphine group. In ambulatory surgical patients, nausea and vomiting is the most common in-hospital complication after ambulatory anesthesia, and is even more common after discharge from the hospital. After discharge, patients no longer have ready access to medical help, and emesis is distressing and interferes with daily tasks (12). Opiates stimulate the chemotactic trigger zone and the vestibular apparatus. The high incidence of nausea and vomiting in the morphine group after discharge may be attributable to the continued effects of morphine on the vestibular apparatus with the increase in activity after the patient is discharged (13).

The study was designed to simulate acute postoperative pain management by nursing staff using IV opioids titrated in multiple doses. The doses chosen were based on a protocol described by Wetchler (7) and comparable to those used in other studies (14,15) with a view to safety if administered by nursing staff. These are relatively small doses. The fact that it took 20 minutes to achieve a statistically significant decrease in baseline scores in both groups and 40 minutes to achieve VAS pain scores less than 40 mm, suggests that such regimens are not achieving their goal in providing rapid control of acute postoperative pain. Larger doses may have produced a more rapid control, but at the risk of incurring a greater incidence of side effects, such as respiratory depression.

No previous study has compared morphine and fentanyl for the treatment of postoperative pain after ambulatory surgery. Pandit and Kothary (14) compared morphine, fentanyl, meperidine, and sufentanil for IV premedication in outpatients. Morphine and fentanyl were comparable with respect to recovery discharge times and side effects. There was a higher incidence of discomfort on injection with morphine and a higher incidence of nausea and vomiting which did not reach statistical significance. This may reflect the use of a smaller total dose of opiate and use of prophylactic antiemetics in their study. Pandit et al. (16) compared fentanyl and butorphanol, an opiate with a duration of action similar to morphine, as a supplement to balanced anesthesia in outpatients. In the fentanyl group, there was a higher incidence of severe postoperative pain and the need for more analgesia. The incidence of nausea and vomiting was similar.

The anesthesiologist is increasingly required to choose anesthetics which are cost-effective. Therefore cost is increasingly a concern. Based on our pharmacy price for the drugs used in this study fentanyl cost \$0.93 per 100-μg ampule, morphine, \$0.19 per 10 mg ampule, and acetaminophen with codeine, \$0.05 per tablet. Totaling the cost of all ampules opened for each patient and the tablets used, the average cost per patient for analgesics in the morphine group was five times less expensive than the fentanyl group, \$0.24 versus \$1.36. When the cost of the antiemetic medication ondansetron (\$18.07) is included the average cost per patient for postoperative treatment for the morphine group was \$4.61 versus \$3.85 for the fentanyl group. In this study, ondansetron which has no sedative properties was used as an antiemetic. The use of more conventional antiemetics would have resulted in a lower average cost per patient for the morphine group. Postdischarge nausea and vomiting may also incur cost on the patient as medicines for its treatment may be purchased (12). Conventional antiemetics have side effects. Thus a study comparing morphine and fentanyl with a combination of these antiemetics may have yielded different recovery results.

In conclusion, in the protocol used in this study, morphine and fentanyl were equally effective in the management of acute postoperative pain after painful ambulatory surgical procedures in Phase I, but fentanyl was associated with higher pain scores and the need for additional oral analgesia during Phase II recovery when compared with morphine. Morphine produced a better quality of analgesia than fentanyl during the hospital stay and was not associated with

delays in fitness for discharge. The incidence of opiate-related side effects in-hospital was similar in the two groups. Morphine was, however, associated with a higher incidence of postdischarge nausea and vomiting. If fentanyl is used to control immediate postoperative pain in the PACU in patients undergoing painful ambulatory procedures, oral analgesics should be given as supplements.

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