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Comparison of the Effect of Intraoperative Morphine and Fentanyl on Discharge Readiness in Patients Undergoing Elective Day-Case Endoscopy: A Natural Experiment

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Abstract

Objective: This study assessed whether morphine, compared to fentanyl, delayed fitness for discharge in patients undergoing day-case gastrointestinal (GI) endoscopy.

Materials and methods: Using a retrospective observational design with a natural experiment framework, we compared two groups created by unpredictable fentanyl shortages that prompted morphine use without changes to caregivers or care: the fentanyl and the morphine groups. Data came from pre-anesthetic, intraoperative, and post-anesthesia care unit (PACU) records at Srinagarind Hospital, Khon Kaen University, from January 2021 to December 2022. The primary outcome was time from PACU arrival to a post-anesthetic discharge scoring system (PADSS) score of 9 or more. Secondary outcomes were the PADSS sub-categories: vital signs, post-anesthetic activity, postoperative nausea and vomiting (PONV), pain, and surgical bleeding. Analyses used Kaplan-Meier survival analysis.

Results: Of the 442 patients (286 in the fentanyl group and 156 in the morphine group), the proportion achieving a PADSS score of 9 or more by 75 min was significantly higher in the fentanyl group ($P < 0.001$), but no significant differences remained at 90 min or later. The 75-min difference persisted after adjustment for opioid dose. Among sub-categories, patients in the fentanyl group reached full marks sooner in vital signs ($P < 0.001$) and activity ($P < 0.001$), with no significant differences in PONV ($P = 0.81$), pain ($P = 0.62$), or surgical bleeding ($P = 0.16$).

Conclusion: In day-case GI endoscopy, discharge readiness at 75 min was more frequent with intraoperative fentanyl than morphine; no significant difference was detected thereafter.

Keywords: ambulatory surgical procedure, endoscopy, fentanyl, morphine, procedural sedation

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Introduction

Delayed awakening from anesthesia remains one of the most significant challenges an anesthesiologist faces.[1] It commonly involves altered mental status and respiratory compromise leading to increased morbidity, operating room delays, and increased cost.[2] Among the principal factors responsible for delayed awakening following anesthesia are anesthetic agents and medications used in the perioperative period.[1,3] Opioids are commonly used during operations to provide analgesia and sedation. Their clinical effects can vary greatly between subjects and can be difficult to predict.[4] Thus, opioids can be a source of delayed awakening, especially when their effects do not match with the clinical needs. Adequate recovery time and awareness of rare side effects increase in importance as day-case surgery continues to gain popularity.[1,5] Because of this, mismatching of opioids and clinical needs is a crucial problem.

At Srinagarind Hospital, a day-case endoscopic patient usually undergoes anesthesia with intravenous sedation consisting of propofol for sedation and an opioid for analgesia. The most common opioid used for day-case endoscopy is fentanyl, due to its fast onset and short duration.[4,6] However, fentanyl shortage is a recurring issue, and from time to time, anesthesiologists are forced to use morphine when fentanyl is not available, despite its slower onset and longer duration compared to fentanyl.[7] Some anesthesiologists and nurse anesthetists are understandably concerned with using morphine instead of fentanyl for day-case patients, as the former may potentially cause increased recovery time, delayed discharge, operating room delay, and healthcare costs. Bhagat et al. reported that the mean time to emergence of patients undergoing supratentorial craniotomy was not statistically different between the morphine and fentanyl groups.[8] Another study performed by Sanford et al. showed that the times to return of spontaneous movement, response to voice, and appropriate response to a voice command in patients undergoing cardiac surgery were not significantly different between the morphine and fentanyl groups.[9] Few studies have compared the time to emergence between morphine and fentanyl, even as drug shortages continue as persistent problems.[10]

The studies mentioned above provide some insights that contradict conventional understanding regarding the benefits of fentanyl over morphine on patients' speed of recovery, hinting that despite different pharmacological profiles, fentanyl and morphine may yield similar effects in clinical practice. However, both studies involved long procedures. With prolonged or repeated administration, fentanyl accumulates and its context-sensitive half-time lengthens, so its offset advantage over morphine diminishes[11]; in addition, emergence after such procedures may occur long after the initial opioid dose, when the effects of both drugs have already waned. These conditions may explain why no difference was found. By contrast, gastrointestinal (GI) endoscopy is a short procedure in which differences in onset and offset between the two opioids would fall within the early recovery period, and to our knowledge, no study has compared fentanyl

and morphine in this setting.

The present study aimed to investigate whether there were differences in time to discharge readiness between patients treated with fentanyl and morphine using retrospectively collected data. The null hypothesis was that the time to discharge readiness, defined as a post-anesthetic discharge scoring system (PADSS) score of 9 or more, would not differ between the two opioids.

Materials and methods

As a retrospective observational study, the present study utilized the natural experiment design.[12] At the study site, fentanyl shortages had occurred over the years, forcing anesthesiologists to use morphine instead. As these shortages did not occur with any predictability, nor did they cause any changes in practice other than the switch to morphine, there was no reason to expect systematic differences in patient characteristics; baseline characteristics of the two groups are compared in Table 1. Likewise, there was no reason to believe that other factors, including those of healthcare practitioners, were any different from when there were no fentanyl shortages. This is the concept of a natural experiment, where a random occurrence causes different groups of subjects to receive different treatments, even though other factors are held constant. Due to this setup, the patients who were given fentanyl could be compared with those who received morphine (those who happened to receive care during fentanyl shortages).

The data were collected from Srinagarind Hospital, Faculty of Medicine, Khon Kaen University during the years 2021 and 2022. Patient records were searched manually by one of the researchers, and all records that matched the inclusion and exclusion criteria were separated for data entry. Patient demographics, surgical information, details on the intra-

Table 1 Patient characteristics

	Group F (n=286)	Group M (n=156)	*P*-value
Sex, n (%)			0.930
Male	140 (49.0)	77 (49.4)	
Female	146 (51.0)	79 (50.6)	
Age (yr)	61.2 ± 12.3	58.5 ± 14.1	0.045*
ASA classification, n (%)			0.140
I	51 (17.8)	37 (23.7)	
II	235 (82.2)	119 (76.3)	
Weight (kg), mean ± SD	58.7 ± 10.5	56.2 ± 11.3	0.023*
Duration of operation (min), mean ± SD	38.4 ± 18.7	35.2 ± 16.9	0.068

Values are n (%) or mean ± standard deviation. Group F, fentanyl; Group M, morphine; ASA, American Society of Anesthesiologists

operative period, details on patients' recovery in the post-anesthesia care unit (PACU), and the patients' PADSS scores were included. In accordance with institutional protocol, patients remained in the PACU for at least 60 min before discharge eligibility was assessed; PADSS was first assessed 60 min after PACU arrival and every 15 min thereafter. The data-extraction form recorded the first time at which each PADSS component reached 2 from the 60-min assessment onward, and the first time at which the PADSS score was 9 or more in categories beginning at 75 min, so a patient meeting the discharge criterion at the 60-min assessment was classified at 75 min. The total intraoperative opioid dose was extracted from the anesthetic record in micrograms for fentanyl and milligrams for morphine. Weight-normalized doses were calculated by dividing the total dose by body weight.

To compare opioid exposure between groups, doses were converted to intravenous morphine milligram equivalents (MME). The primary analysis used a fentanyl-to-morphine potency ratio of 100:1 (fentanyl 100 μg IV ≈ morphine 10 mg IV).[13] Because published equianalgesic ratios for intravenous fentanyl vary, a ratio of 50:1 was used as a sensitivity analysis. Equianalgesic ratios reflect relative analgesic potency and were used to place the two opioids on a common dosing scale. This study was approved by the Khon Kaen University Ethics Committee in Human Research (HE661334). Because the study was retrospective and used anonymized data, the committee waived the requirement for informed consent. Inclusion criteria were day-case endoscopy under sedation, age 18 years or older, and American Society of Anesthesiologists (ASA) physical status I–III. Exclusion criteria were admission before endoscopy or planned admission after endoscopy; sedation with drugs other than propofol, morphine, or fentanyl; allergy to morphine or fentanyl; underlying diseases interfering with drug metabolism, e.g., liver disease, renal impairment, or hypothyroidism; preexisting neurological or psychological conditions; a history of substance or alcohol use; and missing data required for the study.

The primary outcome was discharge readiness, based on the PADSS; a patient was deemed fit for discharge when his or her PADSS score was equal to or greater than 9.[14] The secondary outcomes were the five PADSS components: vital signs (blood pressure and heart rate), post-anesthetic activity, postoperative nausea and vomiting and requirement of antiemetic drugs, postoperative pain and requirement of analgesics, and surgical bleeding in the PACU. All eligible patients during the study period (1 January 2021 to 31 December 2022) were included: 442 patients, of whom 286 received fentanyl and 156 received morphine.

Statistical analysis

The primary outcome was the time from PACU arrival to discharge readiness, defined as the first assessment at which the PADSS score was 9 or more. Assessments were recorded up to 120 min after PACU arrival; a patient not meeting the criterion by then would have been censored at 120 min, that is, counted as under observation until that time without the event being recorded. For each secondary outcome, the event was the first assessment at which the

corresponding PADSS component reached 2, with the same censoring rule. Time to each outcome was described with Kaplan-Meier curves, which show the cumulative proportion of patients not yet meeting the criterion at each assessment time, and the groups were compared with the log-rank test. Kaplan-Meier analysis was used to describe the full time course of recovery, recognizing that with assessments at 15-min intervals it approximates a comparison of proportions at those times. The cumulative proportions of patients ready for discharge at 75 and 90 min were therefore also compared, reported as risk differences with 95% confidence intervals and tested with the χ^2 test or, when an expected cell count was below 5, Fisher's exact test.

All *P*-values are reported to two significant figures, with values below 0.001 reported as $P < 0.001$. A Cox proportional hazards model was considered as a summary of the treatment effect but was not used, because the proportional hazards assumption was not met (Schoenfeld residual test, $P < 0.001$). For each PADSS component, the cumulative proportion of patients reaching a score of 2 by 75 min was also compared as a risk difference with a 95% confidence interval and tested as for the primary outcome. These comparisons were exploratory and were not adjusted for multiple testing. Statistical analysis was performed using R version 4.1.0. Continuous variables were presented as mean ± SD or median [IQR], and categorical variables as n (%). Continuous variables were compared with Welch's t-test and categorical variables with the χ^2 test. Opioid doses were compared between groups with the Mann-Whitney U test.

For the primary outcome, the time from PACU arrival to a PADSS score of 9 or more was used to estimate the Kaplan-Meier curve for each group. The life table reported, for each assessment time, the number of patients at risk, the number meeting the criterion, the proportions meeting and not meeting it during the interval, and the cumulative proportion not yet meeting it. The cumulative proportions ready for discharge at 75 and 90 min were compared as risk differences with 95% confidence intervals. *P*-values < 0.05 were considered statistically significant. For the secondary outcomes, the time from PACU arrival to meeting the criterion (a score of 2) on each PADSS component was used to estimate the Kaplan-Meier curve for each group. Life tables were reported for the vital signs and activity components, showing, for each assessment time, the number of patients at risk, the number meeting the criterion, the proportions meeting and not meeting it during the interval, and the cumulative proportion not yet meeting it. Groups were compared with the log-rank test, with $P < 0.05$ considered statistically significant. To adjust for opioid dose, the proportion of patients reaching a PADSS score of ≥ 9 by 75 min was modeled with logistic regression, with treatment group as the exposure and MME per kg as a covariate. Separate models were fitted for the 100:1 and 50:1 conversion ratios and repeated with additional adjustment for age, sex, ASA physical status, and operation time. Results were reported as odds ratios with 95% Wald confidence intervals.

Results

A total of 442 patients met the study's criteria, with 286 patients in the fentanyl group and 156 in the morphine group. Patients in the fentanyl group were older (mean 61.2 vs 58.5 yr; P = 0.045) and heavier (58.7 vs 56.2 kg; P = 0.023) than those in the morphine group; sex, ASA physical status, and duration of operation did not differ significantly (Table 1). No patient was censored for the primary outcome; all 442 patients reached a PADSS score of 9 or more within 120 min. For the secondary outcomes, one patient in the morphine group was censored for each of activity and nausea and vomiting. At the first assessment, 60 min after PACU arrival, 13 of 442 patients (2.9%; 6 in the fentanyl group and 7 in the morphine group) had reached a score of 2 on at least one PADSS component, and no patient had reached it on all five. Consequently, at most one patient in each group could have met the discharge criterion at that assessment.

Intraoperative opioid doses are shown in Table 2. Patients in the fentanyl group received a median of 50 µg (IQR, 25-50) of fentanyl, and those in the morphine group a median of 3 mg (IQR, 2.75-4.00) of morphine. At a conversion ratio of 100:1, the fentanyl group received more opioid per kg than the morphine group (median MME 0.077 vs 0.052 mg/kg; $P < 0.001$); at 50:1, it received less (0.038 vs 0.052 mg/kg; $P < 0.001$). Time to discharge readiness differed between groups (log-rank $P < 0.001$), although the median time to discharge readiness was 75 min in both groups (Table 3 and Figure 1). By 75 min, 276 of 286 patients (96.5%) in the fentanyl group and 131 of 156 (84.0%) in the morphine group had reached a PADSS score of 9 or more (risk difference 12.5% points; 95% CI, 6.9 to 19.3; $P < 0.001$). This difference persisted after adjustment for MME per kg (100:1: OR 6.22; 95% CI, 2.71 to 14.30; 50:1: OR 4.00; 95% CI, 1.74 to 9.23) and after further adjustment for age, sex, ASA physical status, and operation time (100:1: OR 5.61; 95% CI, 2.45 to 12.84; 50:1:

Table 2 Intraoperative opioid dose

Opioid dose	Group F (n=286)	Group M (n=156)	*P*-value
Fentanyl dose (µg)	50 [25-50]	-	-
Fentanyl dose (µg/kg)	0.77 [0.58-0.93]	-	-
Morphine dose (mg)	-	3 [2.75-4]	-
Morphine dose (mg/kg)	-	0.052 [0.042-0.065]	-
MME (mg/kg; 100:1)	0.077 [0.058-0.093]	0.052 [0.042-0.065]	< 0.001*
MME (mg/kg; 50:1)	0.038 [0.029-0.046]	0.052 [0.042-0.065]	< 0.001*

Values are median [IQR]. Group F, fentanyl; Group M, morphine. *P*-values are from the Mann-Whitney U test. MME, intravenous morphine mg equivalents, calculated at a fentanyl-to-morphine ratio of 100:1 (primary) or 50:1 (sensitivity analysis).

Table 3 PADSS

Opioid treatment	Time from PACU arrival (h:min)	Number at risk	Number meeting criterion	Proportion during interval		Cumulative proportion not yet meeting criterion
				Met	Not met	
Fentanyl	01:00	286	0	0.000	1.000	1.000
	01:15	286	276	0.965	0.035	0.035
	01:30	10	9	0.900	0.100	0.003
	01:45	1	1	1.000	0.000	0.000
	02:00	0	0	-	-	0.000
Morphine	01:00	156	0	0.000	1.000	1.000
	01:15	156	131	0.840	0.160	0.160
	01:30	25	23	0.920	0.080	0.013
	01:45	2	2	1.000	0.000	0.000
	02:00	0	0	-	-	0.000

Criterion: PADSS score of 9 or more, denoting fitness for discharge

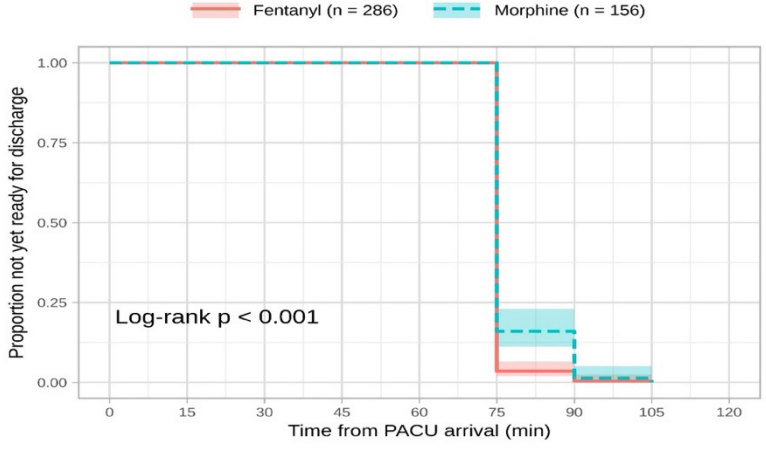


Figure 1 Time to discharge readiness by opioid group. Kaplan-Meier curves of the proportion of patients not yet ready for discharge (PADSS score < 9) after PACU arrival. Shaded areas indicate 95% confidence intervals.

OR 5.94; 95% CI, 2.32 to 15.21). By 90 min, the corresponding proportions were 99.7% and 98.7% (risk difference 0.9% points; 95% CI, -0.9 to 4.2; P = 0.29).

Among the PADSS components, patients in the fentanyl group reached a score of 2 sooner than those in the morphine group for vital signs (log-rank P < 0.001) (Table 4 and Figure 2) and activity (log-rank P < 0.001) (Table 5 and Figure 3). By 75 min, 98.6% of patients

Table 4 Vital signs

Opioid treatment	Time from PACU arrival (h:min)	Number at risk	Number meeting criterion	Proportion during interval		Cumulative proportion not yet meeting criterion
				Met	Not met	
Fentanyl	01:00	286	0	0.000	1.000	1.000
	01:15	286	282	0.986	0.014	0.014
	01:30	4	4	1.000	0.000	0.000
	01:45	0	0	-	-	0.000
	02:00	0	0	-	-	0.000
Morphine	01:00	156	1	0.006	0.994	0.994
	01:15	155	134	0.865	0.135	0.135
	01:30	21	19	0.905	0.095	0.013
	01:45	2	2	1.000	0.000	0.000
	02:00	0	0	-	-	0.000

A sub-score of 2 is the maximum (normal) score for the vital signs domain of the PADSS. Criterion: vital signs score of 2.

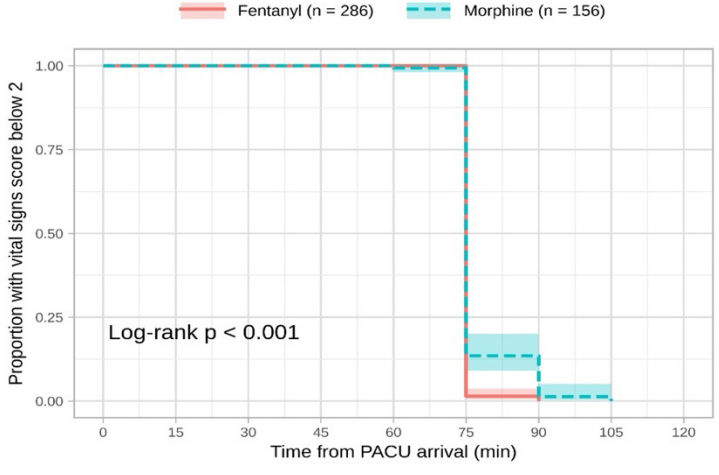


Figure 2 Time to a vital signs score of 2 by opioid group. Kaplan-Meier curves of the proportion of patients whose vital signs score had not yet reached 2. Shaded areas indicate 95% confidence intervals.

in the fentanyl group and 86.5% in the morphine Group had reached a score of 2 for vital signs (risk difference 12.1% points; 95% CI, 7.1 to 18.4; *P* < 0.001), and 97.2% and 87.2%, respectively, for activity (risk difference 10.0% points; 95% CI, 4.9 to 16.3; *P* < 0.001). For nausea and vomiting, the log-rank test did not detect a difference (P = 0.81), but the curves crossed: more patients in the morphine group reached a score of 2 at 60 min (5 of 156 vs 1 of 286), whereas by 75 min the proportion was higher in the fentanyl group (100% vs 96.8%;

Table 5 Activity

Opioid treatment	Time from PACU arrival (h:min)	Number at risk	Number meeting criterion	Proportion during interval		Cumulative proportion not yet meeting criterion
				Met	Not met	
Fentanyl	01:00	286	4	0.014	0.986	0.986
	01:15	282	274	0.972	0.028	0.028
	01:30	8	5	0.625	0.375	0.010
	01:45	3	2	0.667	0.333	0.003
	02:00	1	1	1.000	0.000	0.000
Morphine	01:00	156	0	0.000	1.000	1.000
	01:15	156	136	0.872	0.128	0.128
	01:30	20	19	0.950	0.050	0.006
	01:45	1	0	0.000	1.000	0.006
	02:00	1	0	0.000	1.000	0.006

A sub-score of 2 is the maximum (normal) score for the activity domain of the PADSS. One patient in the morphine group was censored at 120 min. Criterion: activity score of 2.

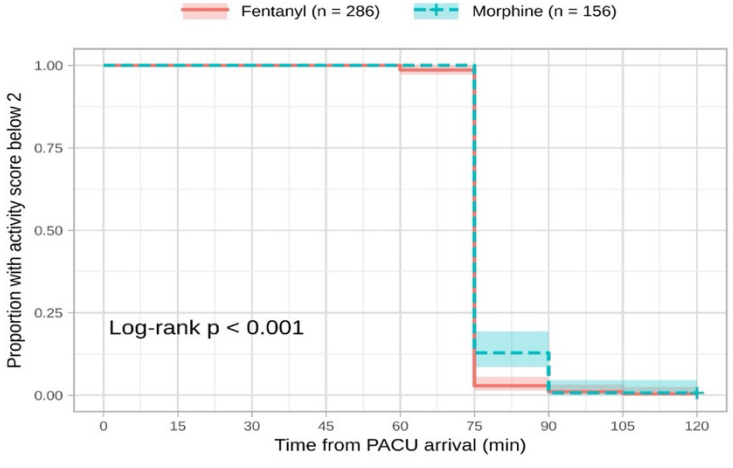


Figure 3 Time to an activity score of 2 by opioid group. Kaplan-Meier curves of the proportion of patients whose activity score had not yet reached 2. Shaded areas indicate 95% confidence intervals. The cross at 120 min marks one censored patient in the morphine group.

risk difference 3.2% points; 95% CI, 0.9 to 7.3; *P* = 0.0053). No statistically significant differences were detected for pain (log-rank *P* = 0.62; risk difference at 75 min 2.2% points; 95% CI, -0.5 to 6.3; *P* = 0.14) or surgical bleeding (log-rank *P* = 0.16), for which all patients in both groups had reached a score of 2 by 75 min.

Discussion

Patients receiving fentanyl reached discharge readiness significantly more often than those receiving morphine by the 75-min assessment. This finding aligned with fentanyl's rapid onset and shorter duration of action, which are often favored in day-case surgeries where swift recovery is ideal.[15] By 90 min after PACU arrival, the difference was no longer statistically significant (risk difference 0.9% points; 95% CI, -0.9 to 4.2). This interval is compatible with no difference but also with an advantage for fentanyl of up to about 4% points, so the data do not establish that the two opioids were equivalent at this time point. Whether the early advantage of fentanyl carries clinical significance may depend on the surgical setting. In high-volume endoscopy units, where turnover time between cases is critical, even a 15-min delay could disrupt workflow. For hospitals facing fentanyl shortages, as in this study, morphine may be an alternative where a modest delay in early discharge readiness is acceptable.

The debate over opioid selection for anesthesia is not new, and previous studies have reported inconsistent findings. In cranial and cardiac surgeries, where opioid effects were scrutinized in the context of neurological and hemodynamic stability, researchers such as Bhagat et al.[8] and Sanford et al.[9] found no significant differences in emergence times between morphine and fentanyl. These findings differ from those of the present study, in which a difference was observed at 75 min but not detected at 90 min. This difference may reflect procedure duration, as discussed in the Introduction: in long procedures, differences in onset and offset between the two opioids may dissipate before emergence, whereas in short procedures such as GI endoscopy they fall within the early recovery period.

For the secondary outcomes, patients in the fentanyl group reached full scores for vital signs and activity sooner, whereas the log-rank test detected no statistically significant differences for nausea and vomiting, pain, or surgical bleeding. These findings were consistent with the longer duration of action of morphine, which would be expected to prolong its effects on vital signs and ambulation. Because GI endoscopy does not usually cause lasting pain or significant bleeding, the absence of detectable differences in these outcomes was also expected. The log-rank test did not detect a difference in nausea and vomiting, but by 75 min a small difference favored fentanyl (risk difference 3.2% points), consistent with the greater emetogenicity of morphine.[16]

Opioid dose is a potential confounder in this comparison, because the shortages changed not only the drug administered but possibly also the quantity. The direction of the dose difference depended on the conversion ratio: at 100:1, the morphine group received less opioid, and at 50:1, it received more. Under both ratios, however, the higher likelihood of discharge readiness at 75 min in the fentanyl group persisted after adjustment for weight-normalized dose, suggesting that opioid quantity alone does not explain the difference. A more plausible explanation is the difference in pharmacokinetic profile: the onset and offset

of fentanyl fall within the early recovery period, whereas the slower onset and longer duration of action of morphine extend beyond it.[6,7] For anesthesiologists managing fentanyl shortages, these findings indicate that morphine delays early discharge readiness, although nearly all patients in both groups were ready by 90 min (99.7% and 98.7%, respectively). Where PACU turnover is a constraint, fentanyl may be preferable. Whether these results apply to other day-case procedures, such as orthopedic or gynecologic surgery, and how patient factors such as age or opioid tolerance modify them, should be examined in prospective studies.

There were some limitations in this study. As a retrospective study, it was susceptible to incomplete documentation, missed records, and the inability to control confounding variables. Because PADSS was assessed at 15-min intervals, discharge readiness was known only at assessment times, and the Kaplan-Meier estimates are step functions fixed at these times; with most events occurring at a single assessment, the log-rank test approximates a comparison of proportions at a few discrete time points. In addition, institutional protocol required patients to remain in the PACU for at least 60 min before discharge eligibility was assessed, so recovery during the first 60 min could not be described, and differences between the groups during that period may have been attenuated. Moreover, the absence of a statistically significant difference at 90 min should not be interpreted as evidence that the two opioids are equivalent: no equivalence margin was prespecified, and comparisons beyond 90 min were uninformative because only one patient in the fentanyl group and two in the morphine group had not yet reached discharge readiness. Finally, although the timing of the shortages was unpredictable, patients in the Fentanyl Group were older and heavier than those in the Morphine Group, so the natural-experiment assumption of comparable groups was not fully met. Older age would, if anything, be expected to slow recovery in the Fentanyl Group, and the difference at 75 minutes persisted after adjustment for age, sex, ASA physical status, operation time, and weight-normalized opioid dose; residual confounding nonetheless cannot be excluded.

Conclusion

In patients undergoing elective day-case GI endoscopy, a higher proportion of patients who received intraoperative fentanyl than of those who received morphine was ready for discharge 75 min after PACU arrival, and this difference persisted after adjustment for opioid dose. No statistically significant difference was detected at 90 min, although equivalence cannot be concluded. Morphine may be an acceptable alternative when fentanyl is unavailable and a modest delay in early discharge readiness is tolerable.

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Author contributions

Phonkrit Soontornwit: conceptualization, methodology, investigation, data curation, formal analysis, writing-original draft. Atipong Pathanasethpong: conceptualization, methodology, supervision, writing-review and editing.

Declaration of conflict of interest

The authors declare no conflict of interest.

AI use acknowledgment

The authors used the Claude Opus 5.0 and 5.5 large-language models to screen for clerical, grammatical, and consistency errors, as well as for phrasing suggestions. Full review, editing and accountability for accuracy are solely the responsibility of the authors.

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