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Post-operative opioid dosing relative to preoperative long-acting opioid dose

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ABSTRACT

INTRODUCTION. Acute post-operative pain treatment continues to pose a primary therapeutic challenge for clinicians, particularly in opioid-tolerant patients. The purpose of this study was to examine whether patients with a high total daily intake of long-acting opioids received the recommended PRN opioid doses in the first 24 hours after surgery.

METHODS. This was a retrospective cohort study using a comprehensive hospital database at the Aarhus University Hospital, Denmark. Patients who received both slow-release long-acting and PRN opioids within the first 24 hours after inpatient surgery were included. Patients were defined as having a high intake if they received slow-release opioids ≥ 60 mg morphine equivalents (MME).

RESULTS. In total, 199 patients (14%) received a 24-hour dose of slow-release long-acting opioids ≥ 60 MME and 1,247 patients (86%) received < 60 MME. The median age was 64 years (interquartile range: 49-74 years); 54% were female. Patients in the ≥ 60 MME group were less likely to receive the recommended first PRN dose (at least 10% of total 24-hour dose) within the first 24 hours after surgery (79 patients; proportion = 0.40, 95% confidence interval (CI): 0.33-0.47 versus 129 patients; proportion = 0.10, 95% CI: 0.09-0.12, $p < 0.001$).

CONCLUSIONS. Our results suggest that patients with a high intake of long-acting opioids may be more likely to receive PRN opioid doses that are not sufficiently adjusted to their total intake during the first 24 hours after inpatient surgery than patients with a lower intake of long-acting opiods.

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TRIAL REGISTRATION. The study was approved by the AUH Ethical Committee and by the Danish Data Protection Agency (ID 1-16-02-341-21).

Despite implementation of novel analgesic strategies over the past two decades, treatment of acute post-operative pain continues to pose a primary therapeutic challenge for clinicians, particularly treatment for opioid-tolerant surgery patients. Opioid-tolerant patients have markedly increased acute post-operative opioid requirements that require immediate-release-as-needed (PRN) opioid dosing to be adjusted accordingly [1, 2]. It has been recommended to administer PRN opioid doses equal to 10-20% of the total daily intake of long-acting opioids [3, 4]. This recommended minimum PRN dose has been widely used in previous studies as a surrogate measure of adequacy, which is considered safe and effective to treat breakthrough pain [1, 4, 5].

However, evidence suggests that PRN opioids for treatment of moderate to severe acute post-operative pain may

be underdosed among opioid-tolerant patients, resulting in poorly controlled pain and associated health risks [6, 7]. Few previous studies have examined PRN opioid dosing and adequate pain management among opioid-tolerant patients for breakthrough pain related to cancer [4, 5] and one study has evaluated this topic in the acute post-operative setting [6]. However, these studies included small sample sizes and are out-dated as changes have been introduced to post-operative opioid dosing practices in recent years following increased dosing guidance and oversight [8-11].

Therefore, we decided to examine whether PRN doses among patients with a high total daily intake of long-acting opioids were adjusted in accordance with the patients' total intake of opioids during the first 24 hours after surgery in the surgical ward. This topic is of importance to clinicians as undertreated acute post-operative pain may contribute to delayed recovery, increased morbidity and also progression and development of chronic postsurgical pain, among others [7]. Based on previous evidence, we hypothesised that patients with a total 24-hour intake of slow-release long-acting oral opioids ≥ 60 mg morphine equivalents (MME) were less likely to receive the recommended minimum PRN dose of 10% of their total daily MME in the surgical ward than patients who received < 60 MME.

METHODS

This was a retrospective cohort study of 1,446 adults who underwent inpatient surgery between March 2020 and February 2021 at Aarhus University Hospital (AUH), Denmark. All data were collected from the Business Intelligence (BI) Portal, a database that contains information related to the electronic medical record of patients admitted to the AUH. Patients were included if they received both PRN opioids and slow-release long-acting opioids in the surgical ward following surgery. The 24 hours were measured from the start of surgery because this was the only time point registered in the database. Patients were excluded if they received only one of either PRN or slow-release long-acting opioids. Opioid administrations given perioperatively and at the Post-Anesthesia Care Unit were excluded as refracted/repetitive small doses are often used in this setting. The study was approved by the Ethical Committee at the AUH and the Danish Data Protection Agency (ID 1-16-02-341-21).

Total daily opioid intake

The BI portal database did not contain data about preoperative opioid use. For this study, we therefore dichotomised patients into two groups; patients who received ≥ 60 and < 60 MME of long-acting opioids within 24 hours of the surgery start time. Dicotomisation was based on the assumption that patients who received ≥ 60 MME long-acting opioids in the early post-operative period were likely to have had a high level of preoperative exposure to opioids. This cut-off was supported by the definition for opioid tolerance proposed by the US Food and Drug Administration as a daily consumption of ≥ 60 MME for a minimum of seven days [12].

"As needed" threshold

Previous studies used 10-20% of the total 24-hour opioid intake as a recommended minimum PRN dose [1, 4, 5]. It remains unknown from where this threshold originated. However, it is widely accepted in the literature and clinical setting as the recommended dose for breakthrough pain. We chose a conservative estimate and defined the minimum PRN dose to be at least 10% of the total long-acting opioid dose in the first 24 hours from the start of surgery.

Example: A patient receives 60 MME of slow-release long-acting opioid twice daily. In this case, with a total daily dose of 120 MME, the recommended PRN dose is between 12 (~ 10%) and 24 (~ 20%) MME orally administered or 4-8 MME administered intravenously (IV).

Outcome

The primary outcome was the proportion of patients in the ≥ 60 and < 60 MME groups who received a first PRN opioid dose below the recommended minimum daily MME dose of 10% in the surgical ward within 24 hours of the surgery start time. The first PRN dose was selected as the primary outcome since the first dose is most likely to be under the recommended dose of 10% as second or third doses are likely to be corrected if inadequate. Secondary outcomes included the average of all PRN doses given, the median first PRN dose volume and the number of PRN administrations in the surgical ward.

Statistical analyses

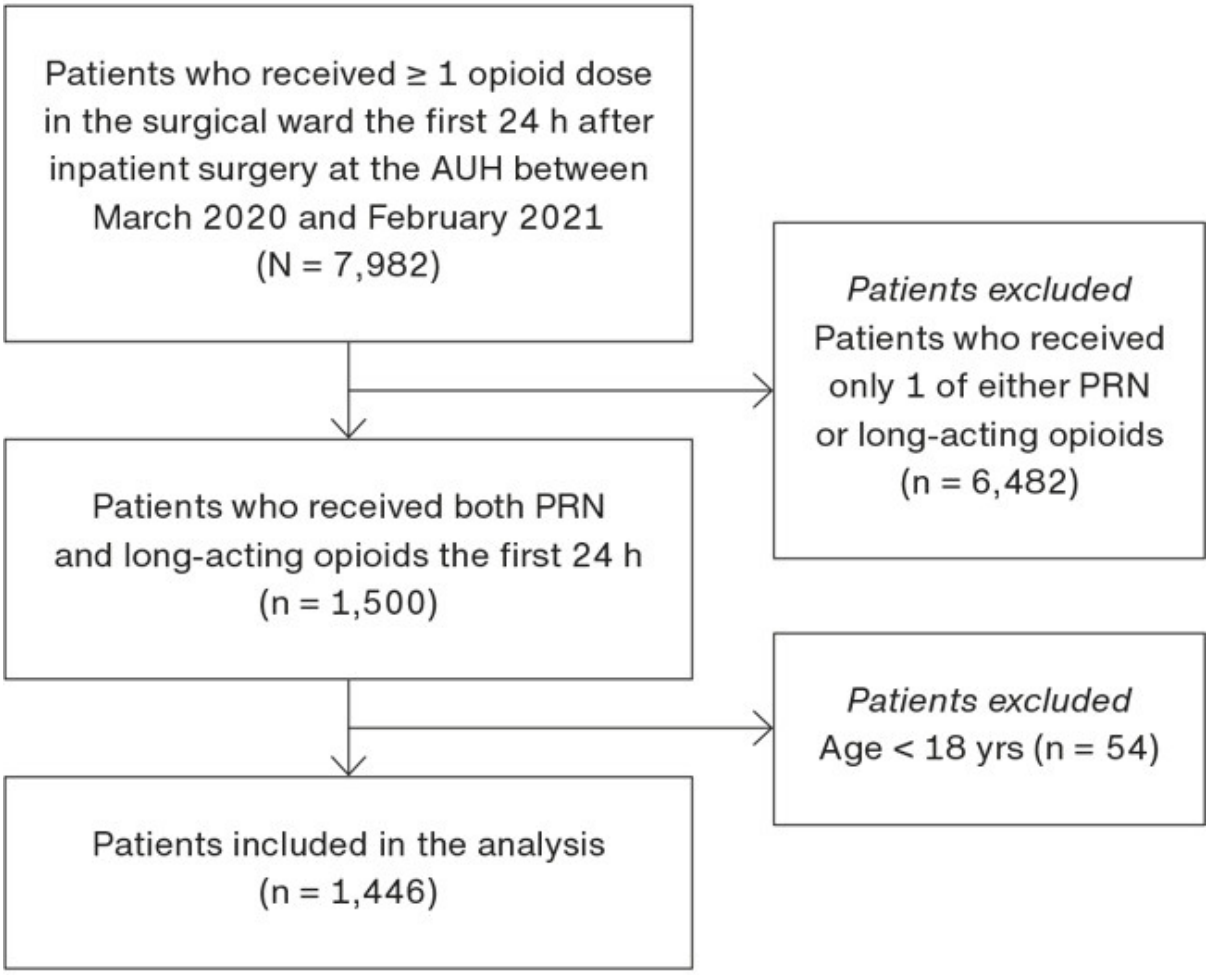
All opioid measurements were converted into MME [13]. Dichotomous variables were presented as numbers (%) with 95% confidence intervals (CI) and compared using the χ^2 test. Depending on variable distributions, continuous variables were either presented as means with standard deviations and compared using either Student's t-test or as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test. Normality of data was assessed visually with QQ-plots and histograms and tested with the Shapiro-Wilk test. Statistical significance was set at two-sided $p < 0.05$. All statistical analyses were conducted using STATA 16 (Stata Corporation, College Station, TX).

Trial registration: The study was approved by the AUH Ethical Committee and the Danish Data Protection Agency (ID 1-16-02-341-21).

RESULTS

Between March 2020 and February 2021, 7,928 adult patients underwent an inpatient surgical procedure at the AUH and received at least one PRN opioid dose in the surgical ward within 24 hours of the surgery start time. Among those, 1,446 patients received both PRN and slow-release long-acting opioids and were therefore included in the analysis (**Figure 1**). The median age was 64 years (IQR: 49-74 years) and 54% were female (**Table 1**). The median length of stay was four days (IQR: 2-9 days).

FIGURE 1 Flow chart for selection of study participants.



AUH = Aarhus University Hospital; PRN = as needed.

TABLE 1 Baseline characteristics of 1,446 patients who received both as-needed opioids and slow-release long-acting opioids within the first 24 hours following surgical procedures at Aarhus University Hospital.

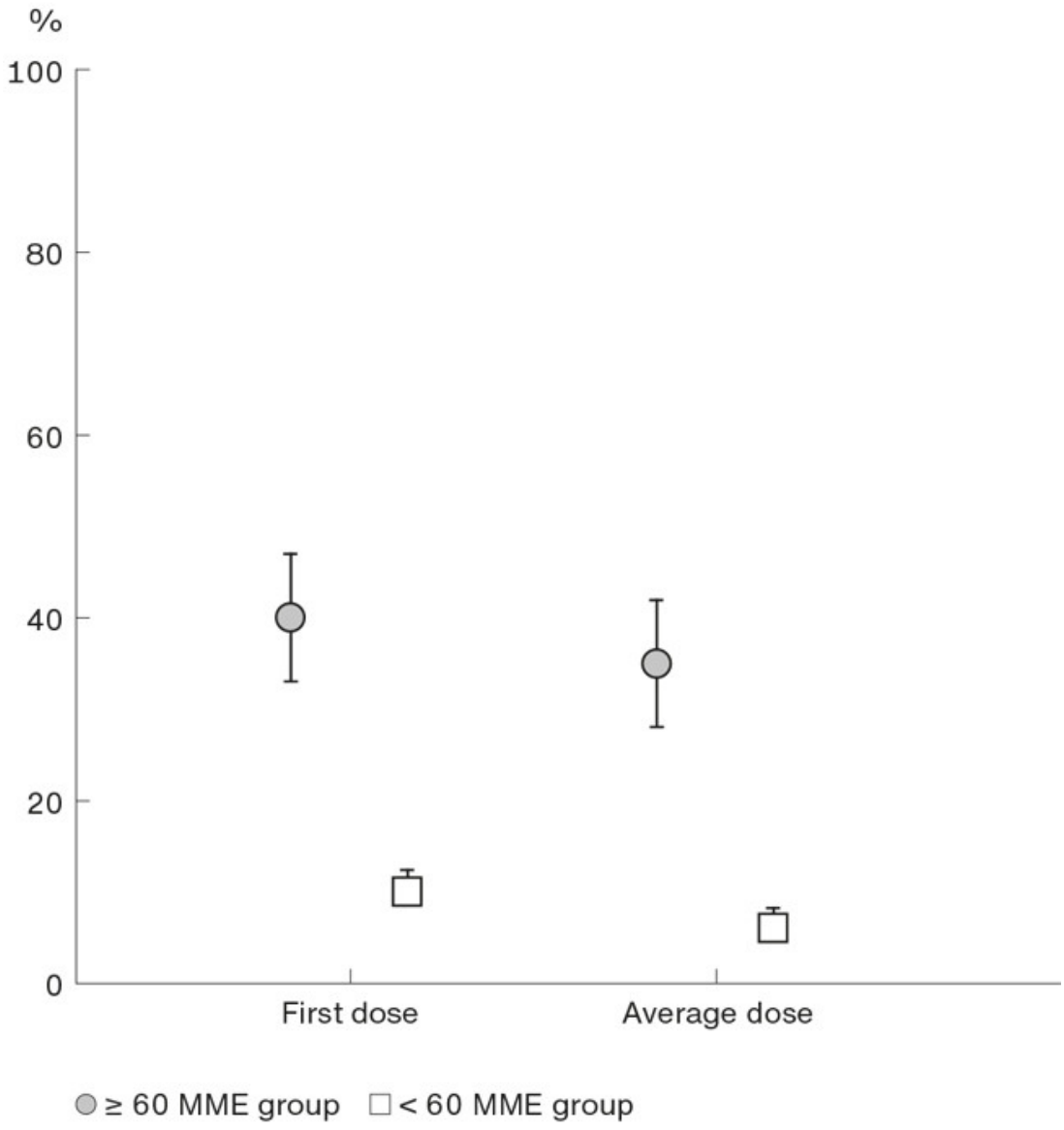
Characteristics	All patients (N = 1,446)	≥ 60 MME group (n = 199)	< 60 MME group (n = 1,247)
Sex, female/male, n (%)	804 (54)/675 (46)	93 (47)/106 (53)	699 (56)/548 (44)
Age, median (IQR), yrs	64 (49-74)	63 (51-72)	64 (49-75)
Length of stay, median (IQR), days	4 (2-9)	7 (3-13)	4 (2-8)
1st PRN dose, median (IQR), MME	10 (7.5-22.5)	15 (10-24)	10 (7.5-15)
Average PRN dose, median (IQR), MME	10 (8.5-15)	15 (10-22.5)	10 (7.5-14)
Surgery type, n (%)			
Orthopaedic surgery	819 (57)	81 (41)	738 (59)
Neurosurgery	281 (19)	46 (23)	235 (19)
General surgery	101 (7)	21 (11)	80 (6)
Cardiothoracic and vascular surgery	92 (6)	24 (12)	68 (5)
Urology	49 (3)	7 (4)	42 (3)
Gynaecology and obstetrics	44 (3)	4 (2)	40 (3)
Interventional cardiology	24 (2)	5 (3)	19 (2)
Otorhinolaryngology surgery	23 (2)	7 (4)	16 (1)
Plastic and breast surgery	13 (1)	4 (2)	9 (1)

IQR = interquartile range; MME = mg morphine equivalents; PRN = as needed.

Within 24 hours of the surgery start time, 199 patients (14%) received a total daily dose of slow-release long-acting opioids ≥ 60 MME, and 1,247 patients (86%) received < 60 MME. The median first PRN dose in the surgical ward was 15 MME (IQR: 10-24 MME) in the ≥ 60 MME group (n = 199) compared with 10 MME (IQR: 7.5-15 MME) in the < 60 MME group (n = 1,247) ($p < 0.001$) (Table 1). The median number of PRN administrations the first 24 hours after surgery start time was three administrations (IQR: 2-5 administrations) in the ≥ 60 MME group compared with two administrations (IQR: 1-4 administrations) in the < 60 MME group ($p < 0.001$).

Patients in the ≥ 60 MME group were less likely to receive the recommended first PRN dose (at least 10% of total daily MME) in the surgical ward than the < 60 MME group (79 of 199 in the ≥ 60 MME group; proportion = 0.40, 95% CI: 0.33-0.47 versus 129 of 1,247 in the < 60 MME group; proportion = 0.10, 95% CI: 0.09-0.12, $p < 0.001$). Patients in the ≥ 60 MME group were also less likely to receive a recommended average PRN dose (calculated as a mean of all given PRN doses) in the surgical ward (69 of 199 in the ≥ 60 MME group; proportion = 0.35, 95% CI: 0.28-0.42 versus 81 of 1,247 in the < 60 MME group; proportion = 0.06, 95% CI: 0.05-0.08, $p< 0.001$) (**Figure 2**).

FIGURE 2 Proportions with 95% confidence interval of patients in the ≥ 60 mg morphine equivalents (MME) group and the < 60 MME group who received below the recommended first and average as needed (PRN) dose during the first 24 h after surgery.



DISCUSSION

In our study, 14% of patients received a total daily dose ≥ 60 MME of long-acting opioids. This is consistent with previous estimates, suggesting that an estimated 15% of patients are opioid recipients going into surgery [14]. Our findings suggest that surgery patients who receive higher daily doses of long-acting opioids may be less likely to receive the recommended minimum dose of 10% than patients who receive lower daily doses of long-acting opioids.

Our main findings are consistent with those of previous studies that examined use of PRN doses among opioid-

tolerant patients. However, most previous studies have been limited to breakthrough pain among cancer patients in non-surgical settings. For example, Patel et al. investigated if opioid-tolerant cancer patients presenting with acute pain exacerbations received recommended initial doses of PRN opioids (defined as ≥ 10% of total 24-hour ambulatory MME) during emergency department visits based on home MME use [5]. In a sample of 216 patients, the authors found that patients with a higher daily home MMEs were at an increased likelihood of being undertreated (77% of patients with < 200 MME, 25% of patients with 201-400 MME and 3% of patients with > 400 MME received adequate PRN doses). Mercadante et al. evaluated the safety and effectiveness of an IV morphine dose equal to 20% of the calculated equianalgesic total daily dose for breakthrough pain in a sample of 48 advanced-stage cancer patients [4]. The authors concluded that IV morphine at a dose equivalent to 20% of the basal oral dosage is safe and effective in the majority of patients who experience episodic pain. Finally, one study examined PRN opioid dosing after surgery. Orgill et al. retrospectively examined PRN opioid dosing among 37 cancer patients after laryngectomy [6]. The authors found that PRN dosing resulted in suboptimal pain control for at least 35% of surgery patients.

Acute post-operative pain management for opioid-tolerant patients may be challenging in several respects. Some barriers to adequate pain management among opioid-tolerant patients include lack of education, limited knowledge of appropriate dosing, poor communication and fear of opioid-related addiction, among others [15, 16]. Acute post-operative pain management in opioid-tolerant patients should be tailored to individual patients following comprehensive screening and assessment including a physical examination, medical and psychiatric history and previous responses to post-operative treatment [17, 18]. Additionally, adherence to evidence-based opioid dosing guidelines alongside sound clinical judgement are necessary to facilitate safe and effective pain management of opioid-tolerant patients who undergo surgery [14, 19, 20].

Limitations

The main limitation is the retrospective nature of this study. Furthermore, we were unable to extract data on preoperative opioid use since this information was not available in the BI Portal database. This information would have allowed us to group patients into preoperative non-users and opioid-users. Also, since pain scores are not recorded in the BI Portal database, we were unable to determine whether the patients' levels of pain was, in fact, acceptable.

CONCLUSIONS

This study was conducted to explore whether post-operative PRN doses among patients with high total daily intake of long-acting opioids were adjusted according to their total intake of opioids during the first 24 hours after surgery. Our findings suggest that patients with a high total daily opioid intake may be less likely to receive PRN opioid doses that are sufficiently adjusted to their daily intake of long-acting opioids during the first 24 hours after inpatient surgery. This may potentially indicate a need for increased awareness about the recommended minimum PRN opioid dosing, particularly among patients with a high total daily intake. This may be achieved through effective and evidence-based clinician education on post-operative opioid-dosing guidelines. Furthermore, prospective research is required to confirm these findings.

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