Comparing oxycodone and morphine in relation to long-term opioid use.

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The aim of this study is to compare oxycodone and morphine as the first-choice opioid for postoperative pain after orthopedic surgery regarding:The proportion of patients with new long-term opioid use (>6 months).The total proportion of...

Ethical review	Not available
Status	Pending
Health condition type	Bone and joint therapeutic procedures
Study type	Interventional research previously applied in human subjects

Summary

ID

NL-OMON57504

Source
Onderzoeksportaal

Brief title
Oxycodone versus morphine - longterm postoperative opioid use

Condition

- Bone and joint therapeutic procedures

Synonym
General orthopedic surgery

Research involving
Human

Sponsors and support

Primary sponsor: Sint Maartenskliniek
Source(s) of monetary or material Support: Sint Maartenskliniek

Intervention

- Medicine

Explanation

N.a.

Outcome measures

Primary outcome

The proportion of patients with new long-term opioid use. Long-term opioid use was defined as the use of any type of opioids, regardless of dose, six months after orthopaedic surgery.

Secondary outcome

On the day of hospital discharge: Daily opioid dose during hospital stay (OMEDD).
Pain score on the day of hospital discharge (NRS). At 6 months postoperatively: The proportion of patients with new long-term opioid use (>6 months).
Daily opioid dose (OMEDD).
Opioid-related side effects.
Pain scores (NRS).

Study description

Background summary

Opioids are effective in the treatment of acute postoperative pain. However, opioid use for acute postoperative pain can unintentionally progress into long-term opioid use with associated adverse consequences, such as serious side effects, opioid tolerance, opioidinduced hyperalgesia, substance abuse and opioid-related mortality [1-3]. The prevalence of long-term opioid use after orthopedic surgery varies widely in the literature (1.4%–24%) [4-9]. A recent study conducted at the Sint Maartenskliniek found that 12.5% of orthopaedic patients continued using opioids long-term after surgery, and 1 in 30 became a new longterm opioid user [10]. This confirms that long-term opioid use remains an issue of concern and highlights the need for preventive intervention.

To address this issue, a working group was established at the Sint Maartenskliniek in late 2022. In response to the publication of the Dutch national guideline Appropriate Opioid Use by the Federation of Medical Specialists (FMS), this group focuses on appropriate opioid use and the development of preventive interventions. A key proposal from the working group is to revise the postoperative pain protocol including the preferred opioid policy.

Globally, oxycodone is the most commonly used opioid, and it is also the first-choice opioid at the Sint Maartenskliniek. However, evidence suggests that oxycodone carries a higher risk of addiction than morphine due to its pharmacological properties [11-13]. Additionally, a Danish study involving over 20,000 patients with hip fractures found that postoperative use of oxycodone was associated with nearly twice the risk of long-term opioid use compared to morphine [7]. Furthermore, several studies have shown that oxycodone and morphine provide comparable pain relief and have comparable side effects, including nausea, vomiting, constipation, and drowsiness [14-20]. Based on these findings, the working group proposed to switch form oxycodone to morphine as the first-choice opioid for postoperative pain management at the Sint Maartenskliniek. This proposal was approved by the hospital's drug committee on May 16, 2023, and will be implemented on September 4, 2023.

Although current literature suggests that morphine carries a lower risk of long-term opioid use compared to oxycodone, there remains a lack of sufficient long-term studies. Therefore, long-term studies are needed to establish an evidence-based first-choice opioid, which can then inform postoperative pain guidelines. The switch from oxycodone to morphine as the first-choice opioid for postoperative pain management presents an opportunity to conduct a prospective study to examine its effect on the development of long-term opioid use.

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2. Brush, D.E., Complications of long-term opioid therapy for management of chronic pain: the paradox of opioid-induced hyperalgesia. J Med Toxicol, 2012. **8**(4): p. 387-92.

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Study objective

The aim of this study is to compare oxycodone and morphine as the first-choice opioid for postoperative pain after orthopedic surgery regarding:

- The proportion of patients with new long-term opioid use (>6 months).
- The total proportion of patients with long-term opioid use (>6 months).
- The daily opioid dose during hospital stay.
- Pain scores in postoperative period and at 6 months.
- The daily opioid dose at 6 months.
- The incidence of side effects at 6 months.

Study design

Study Design

This non-randomized clinical trial includes two cohorts of adult patients who have undergone orthopaedic surgery:

First cohort: Patients treated according to the current postoperative pain protocol, in which oxycodone is the first-choice opioid. Patients who undergo surgery between April 2023 and August 2023 will be eligible for inclusion in this cohort.

Second cohort: Patients treated according to the new postoperative pain protocol, in which morphine is the first-choice opioid. This protocol will be implemented on September 4, 2023. Patients who undergo surgery between September 2023 and January 2024 will be eligible for inclusion in this cohort.

Patient Selection and Invitation

Patients who undergo orthopaedic surgery will be retrospectively selected from the electronic health record system six months postoperatively using a specially developed report. Patients who undergo surgery within three months before the index date, undergo surgery more than three months after the index date, or have not provided consent for scientific research and/or the use of their email address will be excluded.

Eligible patients will receive a personalized email on behalf of the pharmacist at the Sint Maartenskliniek. Since these patients have received medication from the hospital pharmacy, a treatment relationship exists between the pharmacist and the patient, in accordance with the Dutch Medical Treatment Agreement Act (WGBO). The email will contain a brief introduction to the study and a link to a secure, personalized online questionnaire.

Data Collection

The questionnaire consists of the following components:

- Information letter
- Informed consent question
- Pain scores at rest and during movement (NRS)

- A questionnaire on current opioid use (type, dose, and frequency)
- A questionnaire on opioid-related side effects

The questionnaire can only be completed after the patient has provided informed consent.

Completion takes a maximum of 10 minutes.

Additionally, the following data will be extracted from the patient's medical record: Age

- Sex (male/female/other)
- Affected body region (foot/ankle, hip, upper extremity, knee, and spine)
- Pain score at discharge at rest and during movement (NRS)
- Opioid use during hospital stay based on administration records OMEDD)
- Opioid use prior to admission and at discharge

Sample Size Calculation

For the estimation of the effect size of the intervention (the switch from oxycodone to morphine as the first-line postoperative opioid) on new long-term opioid use and the required sample size, the following considerations were made:

- The only study reporting long-term opioid use separately for both morphine and oxycodone is the retrospective cohort study by Simoni et al. (2020) [1]. In this study, conducted among patients with hip fractures, the prevalence of long-term opioid use at one year was 14% among oxycodone users and 9% among morphine users. This study exclusively included opioid-naïve patients, defined as those who had not used opioids prior to the hip fracture.
- Based on the available literature, a small effect size of approximately 0.33 is anticipated for the intervention.
- The baseline risk of new long-term postoperative opioid use in a heterogeneous postoperative orthopedic patient population, as estimated from a previous study conducted at the Sint Maartenskliniek, is 3% [2].
- Given an effect size of 0.33, the expected reduction in the proportion of new long-term opioid users would be from 3% to 2%. To detect this difference, a total sample size of 7,650 patients is required (see table).
- The switch from oxycodone to morphine as first-choice opioid for postoperative pain management is scheduled for September 4, 2023. Consequently, the inclusion of patients in the first cohort is limited to this date. From a practical perspective, it is feasible to begin the inclusion with patients who underwent surgery in April 2023. Therefore, the inclusion in the first cohort can last up to a maximum of five months. Based on previous research at the Sint Maartenskliniek, approximately 400 eligible orthopedic patients are available per month. The response rate in this prior study was approximately 50%. If patients are recruited for five months before and five months after the switch, approximately 1,000 patients can be included in both the first and

second cohorts.
- This results in sufficient power to detect a reduction in long-term opioid use from 3% to 1% (see table).

Expected Reduction (%)	First Cohort (Oxycodone)	Second Cohort (Morphine)	Total Sample Size
3% → 2%	3,825	3,825	7,650
3% → 1%	768	768	1,536

Statistical Analysis Baseline Characteristics

- Descriptive analyses will be conducted regarding baseline characteristics. Potential differences between the cohorts will be considered as confounders in the analysis of the primary outcome.

Primary Outcome

- The proportion of patients with new long-term opioid use (>6 months) in both cohorts will be analyzed using both an intention-to-treat analysis and a per-protocol analysis. The comparison between cohorts will be performed using a chi-square test.

Secondary Outcomes

- The daily opioid dose during the hospital stay will be converted to OMEDD (oral morphine equivalent daily dose) in mg/day. Depending on the data distribution, an appropriate parametric or non-parametric test will be used to compare cohorts.
- The pain score on the day of hospital discharge in both cohorts will be compared using an appropriate parametric or non-parametric test, depending on the data distribution.
- The total proportion of patients with long-term opioid use (>6 months) in both cohorts will be analyzed using both an intention-to-treat analysis and a per-protocol analysis. The comparison between cohorts will be performed using a chi-square test.
- The daily opioid dose after 6 months will be converted to OMEDD (oral morphine equivalent daily dose) in mg/day. The OMEDD values for both cohorts will be analyzed using both an intention-to-treat analysis and a per-protocol analysis. Depending on the data distribution, an appropriate parametric or non-parametric test will be used for comparison.
- The occurrence of opioid-related side effects after 6 months will be dichotomized (yes/no). The comparison between cohorts will be performed using a chi-square test.
- The pain scores after 6 months in both cohorts will be compared using an appropriate parametric or non-parametric test, depending on the data distribution.

1. Simoni, A.H., et al., The association between initial opioid type and long-term opioid use after hip fracture surgery in elderly opioid-naive patients. Scand J Pain, 2020. **20**(4): p. 755-764.

2. Melis, E.J., et al., Long-term postoperative opioid use in orthopaedic patients. Eur J Pain, 2024. **28**(5): p. 797-805.

Intervention

The intervention to be examined in this study will involve the modification of the postoperative pain protocol. In the current protocol, oxycodone is the first-choice opioid, morphine the second choice, and buprenorphine the third choice. In the revised protocol, morphine will become the first-choice opioid, buprenorphine the second choice, and oxycodone the third choice. Switching to the second- or third-choice opioid will occur based on side effects and/or insufficient pain relief. The postoperative pain protocol will follow the WHO pain ladder. In our hospital if there are no contraindications, all postoperative orthopaedic patients admitted to the hospital will receive paracetamol, an NSAID, and a short-acting opioid for postoperative pain management.

Study burden and risks

The burden on participants is expected to be minimal, as they are only required to complete a one-time online questionnaire. The risk associated with the intervention is also considered minimal. The intervention involves switching from oxycodone to morphine as the first-choice postoperative opioid. Both opioids are approved for the treatment of postoperative pain and are included in various national and international guidelines for acute and postoperative pain management [1-3].

1. Dowell, D., et al., CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. MMWR Recomm Rep, 2022. **71**(3): p. 1-95.

2. Hsu, J.R., et al., Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury. J Orthop Trauma, 2019. **33**(5): p. e158-e182.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)
Adults (18-64 years)

Inclusion criteria

Patients who undergo orthopedic surgery and are admitted to the clinical orthopedic department of the Sint Maartenskliniek.

Exclusion criteria

Patients who undergo orthopedic surgery within 3 months prior to or more than 3 months after the index date, or who refuse to be contacted via email or to participate in scientific research.

Study design

Design

Study phase: N/A

Study type:	Interventional research previously applied in human subjects
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Other type of control
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2023
Enrollment:	1600
Duration:	6 months (per patient)
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	morphine (intervention), oxycodone (control)

IPD sharing statement

Plan to share IPD: Yes

Plan description
N.a.

Ethics review

Not available

Date:	11-04-2025
Application type:	First submission
Review commission:	Validatie nWMO registratie door CCMO

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Research portal	NL-009760