Post-operative patient-controlled intravenous oxycodone vs patient-controlled intravenous Piritramide.

A randomized controlled trial.

Dr. Jarne de Mey, dr. Jasper Moonen, dr. Annelies Scholliers, dr. William Alliet, dr. Milica Matic, dr. Tine Opsomer, dr. Domien Vanhonacker.

Author Affiliations:
Department of Anesthesiology and Peri-Operative Medicine University Hospital Brussels (UZ Brussel)
Laarbeeklaan 101, 1090 Brussels
Belgium

Corresponding author:
Dr. Jarne de Mey
Department of Anesthesiology and Peri-Operative Medicine University Hospital Brussels (UZ Brussel)
Laarbeeklaan 101, 1090 Brussels
Belgium
Tel: 0032 486 92 28 04
E-mail: jarne.demey@uzbrussel.be

Author Contributions:
Jasper Moonen and Jarne de Mey were the primary investigators for this study. Annelies Scholliers, William Alliet and Domien Vanhonacker provided valuable feedback during the writing of this article.

Abstract

Introduction: Adequate postoperative pain control is crucial, but choosing the most suitable analgesic approach can be challenging. Intravenous (IV) opioids like morphine, fentanyl, and piritramide are commonly used, while IV oxycodone is less frequently employed. This study aims to comprehensively compare the efficacy and safety of IV oxycodone and piritramide for postoperative pain management.

Methods: This prospective observational study included patients undergoing abdominal or gynecological surgeries. Patient-controlled IV administration of oxycodone or piritramide was used for pain management. Pain scores, adverse reactions, medication usage, and patient satisfaction were evaluated. Statistical analyses including Chi-square tests, Mann-Whitney U tests, and repeated measures ANOVA were conducted.

Results: A total of 74 patients were included in the analysis. No significant differences were found in gender, age, surgical type, or American Society of Anesthesiologists (ASA) class between the two groups. Pain perception scores did not significantly differ between oxycodone and piritramide groups at any time point. However, patients under an oxycodone regime required more boluses to reach the same level of pain control. Adverse events were similar in both groups. Six patients dropped out due to various reasons.

Conclusion: The findings of this study indicate that intravenous oxycodone does not provide superior pain control compared to piritramide following abdominal and gynaecological operations. The oxycodone group demonstrated higher opioid usage and a greater need for boluses. Despite this, oxycodone was found to be a safe postoperative analgesic with low adverse events. These findings contribute to understanding opioid analgesic choices, aiding in improved patient outcomes and better quality of care.

Introduction

Adequate postoperative pain control is a crucial aspect in the field of anaesthesiology. Using the most suitable analgesic approach for the individual patient can be challenging. Comprehensive knowledge regarding the activity profile of different products and their potential side effects is paramount. In the immediate postoperative phase, the intravenous (IV) route stands as the preferred method for administering analgesics. Intravenous administration of opioids ensures a rapid onset of pain relief while exhibiting predictable pharmacokinetics [1].

In European countries IV morphine, Fentanyl, and piritramide represent widely employed options for managing postoperative pain. Conversely, the intravenous administration of oxycodone remains relatively infrequent and has received limited attention as a postoperative analgesic [2]. A noteworthy proportion of German hospitals (approximately nine per cent) have embraced the utilization of IV oxycodone for patient-controlled intravenous analgesia (PCIA) following surgical procedures [1]. By exerting its action on both mu- and kappa opioid receptors, oxycodone is believed to provide supplementary pain relief, particularly in visceral surgery, since kappa receptors are predominantly located on viscera [1,3,4]. Some studies have demonstrated that oxycodone offers superior pain control, fewer adverse reactions, and a faster onset of action as compared to morphine [1]. This unique profile positions oxycodone as a captivating alternative for the management of postoperative pain.

In this prospective randomized trial, our objective is to compare the efficacy and safety of postoperative patient-controlled intravenous administration of oxycodone and piritramide. Through this trial, we aim to provide additional insights into the optimal choice of opioid analgesics for postoperative pain management, helping to improve patient outcomes and to enhance the quality of care provided in clinical practice.

Methods

Overview

This prospective observational study aimed to assess the efficacy and safety of patient-controlled intravenous (IV) administration of oxycodone and piritramide for postoperative pain management in patients undergoing abdominal or gynaecological surgeries, including both laparoscopic and open procedures. The open procedures had no major incision sites. The study was conducted from the 6th of May, 2021, to the 21st of February, 2023. The pain score, measured using the numeric rating scale (NRS), served as the primary outcome measure. Secondary objectives included evaluating adverse reactions, total amount of medication used and patient satisfaction.

Participants

Patients scheduled for abdominal or gynaecological surgery at the University Hospital Brussels (UZ Brussel) were screened for eligibility. The inclusion criteria consisted of individuals aged 18 years or older with American Society of Anesthesiologists (ASA) class I, II, or III. Both laparoscopic and open surgeries were considered for inclusion.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

- History of hypersensitivity or allergic reaction to oxycodone or piritramide.
- Urgent surgical cases (e.g., hemoperitoneum, bowel perforation, gastrointestinal obstruction).
- Presence of conditions that may impact pain perception (e.g., fibromyalgia, psychiatric disorders).
- Liver failure.
- Renal failure with a clearance rate below 10 ml/min.
- Pregnancy or breastfeeding.
- Patients concurrently enrolled in another clinical study.

Ethical Considerations

In adherence to the ethical principles outlined in the Declaration of Helsinki, this prospective clinical trial was randomised controlled. Prior to initiation, the study protocol underwent comprehensive scrutiny and received formal approval from the ethical review board of the UZ Brussel, EudraCT Registry Number: 2020-003682-19. Informed consent was obtained from all individuals prior to their inclusion in the study.

Randomization and Allocation

Eligible patients were approached and provided with detailed information on the study at the anesthesia consultation. After informed consent was obtained patients were enrolled in the study. The study employed simple, non-stratification randomization to randomize patients (via https://www.sealedenvelope.com/) in either an oxycodone or piritramide group. Each patient was assigned a unique patient study number, which was a sequence number based on their enrolment in the trial. Patients were unaware of the group they were assigned to. They received patient-controlled intravenous analgesia (PCIA) without knowledge of the specific drug being administered. To maintain blinding, medication preparation was carried out centrally. The anesthesist and the investigator who filled out the questionnaire knew which medication the patient got. Only the patient was blinded.

Data Collection

The screening period for this study took up to 14 days prior to the surgery. During the screening period, baseline patient characteristics were recorded (e.g. demographic information, ASA class). The baseline visit (D0) marked the start of treatment with the surgical procedure. Day 1 (D1) denotes one day after the operation. During D0 and D1, patients were requested to rate their pain levels on a scale ranging from 0 to 10. A study team member administered the questionnaire at various time points:

- In the Post-Anesthesia Care Unit (PACU) upon the patient's awakening
- One hour after awakening
- Morning of Day 1
- Evening of Day 1

Simultaneously, the study team member recorded the Richmond Agitation-Sedation Scale (RASS) and monitored side effects such as nausea, urinary retention, itching, and constipation. Towards the end of Day 1, patients were asked to assess their satisfaction with the pain management therapy they received. An overview of the study protocol and what was asked and done when can be found in Table 1.

Anaesthesia during surgery

The anaesthesia protocol for the procedure was standardized to prevent post-operative nausea. No premedication was administered. During induction, propofol was titrated to achieve the desired effect, along with the use of sufentanil (10mcg) and rocuronium (0.6mg/kg). Dexamethasone (5mg) was given following intubation. Maintenance of anaesthesia was achieved using propofol (3-6mg/kg/h) and remifentanil (0.1-0.5mcg/kg/min). No additional sufentanil was administered during surgery. The anesthetist on day of surgery was free to change the propofol and remifentanil settings according to their clinical assessment and where free to use a BIS monitor if they wanted to.

To provide supplementary analgesia, patients received 1g of paracetamol and local infiltration of either 20 ml (for male patients) or 15 ml (for female patients) of ropivacaine 7.5mg/mL. The infiltration was injected in the port access places for laparoscopy or injected in the incision site when it was an open procedure. Nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from the protocol due to contra-indications present in many patients and their potential interference with post-operative findings. Approximately 15 minutes before the procedure concluded, a loading dose of intravenous oxycodone (0.06mg/kg, max 6mg) or piritramide (0.09mg/kg, max 9mg) was administered. Ideal body weight (IBW) was used. IBW was determined by subtracting 100 from the length in centimetres for men and subtracting 105 for women.

Patient-controlled intravenous anaesthesia

To ensure equal potency with each button press of the PCIA device, we utilized the morphine Equivalent Dose (MED) when comparing the efficacy of IV oxycodone and IV piritramide. The equianalgesic dose ratio (EDR) between IV morphine and IV oxycodone is 1:1; between IV morphine and IV piritramide, the EDR is 2:3 [5,6,7].

In the recovery ward, patients were equipped with a PCIA device containing either oxycodone or piritramide. The device settings were as follows:

- For group 1, the mixture consisted of 1mg of oxycodone per ml. The bolus dose was set at 2 ml without a continuous dose. A lockout period of 10 minutes was implemented, and the maximum allowed dose within a 4-hour period was 20mg.
- In group 2, the mixture contained 1mg of piritramide per ml. Patients in this group received a bolus dose of 3 ml with the same 10-minute lockout time and absence of a continuous dose. The maximum allowed dose within a 4-hour period was 30 mg of piritramide.

Data Analysis

A total of 80 patients were included in this study, with 40 patients allocated to each study group. The sample size calculation was based on 37 patients per group, and an additional number of patients were included to account for possible dropouts. The study concluded was once a total of 80 patients were enrolled.

Statistical analysis was conducted to assess differences in baseline characteristics (gender, age, ASA score, type of surgery) and outcomes (pain perception, RASS, time until the first bolus, total number of boluses, patient satisfaction, adverse events) between the two groups (oxycodone and piritramide). The significance level was set at 0.05, and various methods were employed, including Chi-square tests, Fisher's exact tests, independent t-tests, non-parametric Mann-Whitney U tests, and Repeated Measures ANOVA.

To asses the comparison of gender, age, ASA class and type of surgery between the 2 groups a Chi-square test and Fisher's exact test was used. To analyse the time until the first bolus and patient satisfaction we used a Mann-Whitney U tests since there were severe outliers in each group. Repeated Measures ANOVA was utilised for time-varying variables such as pain perception and RASS. Post hoc tests with Bonferroni correction were used to compare the groups for each time point separately, but this did not give any changes in significance. Since there was a marginal significant difference between the two 2 groups for age, the models were fitted both with and without age as a confounding variable.

Combined adverse events (nausea, urinary retention, itching, constipation) were assessed by categorizing them as "yes" if they occurred at least once during the study or "no" if they did not occur at any time point. A fisher's exact test was used for each combined adverse event (yes/no) to determine if there were significant differences between the 2 groups.

All analyses were conducted using IBM SPSS.

Results

A total of 80 patients were initially included in the study, with six dropouts observed. Among the dropouts, one patient from each group (oxycodone and piritramide) discontinued participation due to excessive nausea. Additionally, one patient from the piritramide group, who was a known epileptic, experienced an epileptic seizure and received clonidine and diazepam, resulting in withdrawal from the study. Another patient in the oxycodone group did not recall being enrolled in a study upon awakening in the Post-Anesthesia Care Unit (PACU), leading to dropout. In the same group, one patient withdrew after being administered an NSAID and ketamine by the anesthesiologist. Furthermore, one patient from the piritramide group discontinued the study due to a defect with the PCIA device.

Consequently, a total of 74 patients were included in the subsequent statistical analyses. Only one patient had missing values for several variables.

There was no significant difference ($p=0.675$) in gender between the two groups, with 25 famales and 12 males in the oxycode group compared to 24 females and 13 males in the piritramide group. Similarly, there was no significant difference in age between the groups ($p=0.055$). However, it is worth mentioning that there was a marginal significant difference, the patients in the oxycodone group were older, with a difference of 7,5 years. Among the four types of surgeries performed (laparoscopic abdominal, laparoscopic gynaecological, open abdominal, and open gynaecological), no significant difference in the distribution of surgical types between the groups ($p=0.944$) was found. Notably, the open abdominal surgeries exclusively involved eventration cure procedures and did not include any major incisions. The open gynaecological surgeries where open hysterectomies with a small incision.

Furthermore, there were no significant differences in the distribution of ASA class between the groups (p=0.427). Table 2 gives an overview of the different types of surgery per group.

No significant differences were observed between the two groups regarding pain perception at each time point individually or in total. Even after incorporating age as a factor in the analysis, there remained no significant differences in pain perception between the two groups. Figure 1 shows the Mean NRS over time for the 2 groups in a graph.

No significant differences were found between the two groups regarding RASS scores at each time point individually or in total. Even after adjusting for age in the analysis, no significant differences were observed in RASS scores between the two groups. Figure 2 shows the Mean RASS over time for the 2 groups in a graph.

Regarding the time until the first bolus, no significant differences was found between the two groups ($p = 0.084$). Also significant differences in patient satisfaction between the two groups was found ($p = 0.477$).

A significant difference was observed in the number of boluses administered, with the oxycodone group receiving more boluses than the piritramide group ($p = 0.024$). This significant difference persisted even after accounting for age in the analysis. The mean number of boluses in the oxycodone group was 17.32, whereas, in the piritramide group, it was 11.47. In terms of dosage, each bolus in the oxycodone group was 2mg, resulting in a mean use of 34.64mg of oxycodone, equivalent to 34.64mg of morphine. In contrast, each bolus in the piritramide group was 3mg, leading to a mean use of 34.41mg of piritramide, equivalent to 22.94mg of morphine. Table 3 shows the mean total boluses received per group over the time of the study.

There were no significant differences between the two groups in terms of nausea, urinary retention, itching, and constipation. In the oxycodone group 8 people reported nausea, while in the piritramide group 12 people reported nausea. No instances of urinary retention were observed in the oxycodone group, while one person reported urinary retention in the piritramide group. None of the individuals in the oxycodone group reported itching, whereas one person in the piritramide group reported itching. In the oxycodone group 3 of the patients reported constipation while 5 patients in the piritramide group reported constipation.

Discussion

This study aimed to compare the effectiveness and safety of IV oxycodone with IV piritramide for postoperative pain control in abdominal and gynaecological surgery. Our rationale for conducting this study was based on the potential advantages of IV oxycodone, particularly its action on kappa opioid receptors, which may offer additional pain relief in visceral surgery. Our review of prior studies

comparing oxycodone to other opioids revealed evidence suggesting that oxycodone may provide better pain control with fewer side effects compared to opioids such as morphine or piritramide.

In a study conducted in Germany between 2005 and 2012, Sebastian et al. [5] conducted a randomized trial involving approximately 7000 surgical patients. The patients were divided into two groups: one received a PCIA system utilizing piritramide, and the other received an analogous PCIA system employing oxycodone. The study encompassed patients undergoing abdominal, gynaecological, orthopaedic, and trauma surgeries [5]. To our knowledge, this study is the sole investigation specifically comparing piritramide with oxycodone. The evaluation of patient satisfaction revealed similar levels of contentment in both groups, with 96.7% of the piritramide group reporting good to very good satisfaction, compared to 98.9% in the oxycodone group. However, the oxycodone group exhibited significantly fewer side effects (6.7% versus 12.7%, $p < 0.01$). Nausea was observed in 4% of patients receiving piritramide, in contrast to only 2% of patients receiving oxycodone. Furthermore, vomiting occurred in 6% of piritramide patients versus 2% of oxycodone patients. Somnolence was also reported at a higher rate in the piritramide group (1%) compared to the oxycodone group (0.6%).

The study's conclusion indicated that both piritramide and oxycodone exhibit comparable effectiveness in providing analgesia. However, oxycodone demonstrated a marked advantage by exhibiting significantly fewer typical opioid side effects.

In a study conducted by Lenz et al. [3], 91 patients who underwent a laparoscopic hysterectomy were included and randomly assigned to two groups. At the end of the surgery, both groups received a loading opioid dose of 0.07 mg/kg. After the surgery, patients were given a PCIA system containing either morphine or oxycodone. The oxycodone group exhibited a reduced need for medication and displayed lower NRS pain scores at 30 minutes and one hour following the surgical procedure. Furthermore, the oxycodone group experienced a delayed time to the administration of their first self-administered dose post-surgery. Moreover, over the course of the first 24 hours, the total dose of oxycodone administered was substantially lower compared to the morphine group (13.3 +/- 10.4 mg vs. 22.0 +/- 13.1 mg, $P = 0.001$).

While the occurrence rates of nausea and vomiting were similar in both groups, the oxycodone group demonstrated significantly less sedation within the initial 24 hours following the surgery [3]. These findings highlight the potential advantages of IV oxycodone over IV morphine in the context of laparoscopic hysterectomy.

In a study conducted by Silvasti et al. [8], patients undergoing reconstructive surgery of the breast or major vertebrae operations (e.g., spinal fusion) were administered either a morphine or oxycodone PCIA system. The bolus doses used in this study were 45 mcg/kg of morphine and 30 mcg/kg of oxycodone. Surprisingly, despite the differing doses, the patients in both groups utilized similar amounts of morphine and oxycodone, with no discernible difference in the quality of analgesia or the occurrence of side

effects. Based on these findings, the study concluded that the two drugs appear to be equipotent in this specific type of surgery.

Emerging evidence suggests that in the context of visceral surgery, the equipotency of oxycodone compared to morphine may lean towards a ratio of 2:3, taking into account its additional action on kappa receptors [3,9]. In a study conducted by Kalso et al. [9], 39 patients who underwent major abdominal surgery were administered either IV morphine or oxycodone in doses of 0.05 mg/kg. The dosing interval was set at five minutes, allowing patients to request analgesics until they no longer required them. Results revealed that oxycodone achieved the "first state of pain relief" faster than morphine (28 minutes vs. 46 minutes) and provided a longer duration of pain relief (39 minutes vs. 27 minutes). Furthermore, the total dose required during the 2-hour study period was lower for oxycodone (21.8 mg vs. 34.2 mg). In terms of side effects, morphine exhibited higher sedation levels and a greater reduction in mean arterial blood pressure compared to oxycodone.

Another study by Tao et al. [10] explored the use of oxycodone not only as a postoperative drug but also as an intraoperative analgesic. The study involved 220 patients undergoing gynaecological laparoscopic surgery, who were divided into two groups: one receiving oxycodone during surgery and the other receiving sufentanil. Both medications maintained stable hemodynamics during the surgery, and the groups had no significant difference in postoperative analgesia. However, the oxycodone group experienced a 13.5% lower incidence of postoperative nausea and vomiting (PONV) compared to the sufentanil group (38.8% vs. 25.3%, $p = 0.04$).

Overall, these findings suggest that the use of oxycodone, both during and after surgery, may offer benefits such as reduced postoperative cognitive dysfunction[11] and a lower incidence of PONV compared to sufentanil, used peroperatively. The side effects of oxycodone are those typical of strong opioids i.e. central nervous system (CNS) depression, respiratory depression and constipation. There is no conclusive evidence that oxycodone causes more or less respiratory depression as compared to morphine. However, there seem to be fewer hallucinations, nightmares and pruritus. [1]

Some differences were seen between the studies. Sebastian et al reported that there was less nausea and somnolence in the oxycodone group compared to the piritramide group. While Lenz et al. [3] and Silvasti et al. [8] reported no differences in nausea and vomiting, although they compared oxycodone with morphine and not piritramide. It was also found that different studies suggested different potency of oxycodone compared to morphine. Silvasti et al. found an equipotency between morphine and oxycodone. [8] While a study by Lenz et al. even proposed that oxycodone was more potent than morphine for visceral pain relief.[3]

Oxycodone bioavailability ranges from 100% intravenously to 60-80% orally, with less than 20% sublingually. The drug is primarily metabolized by CYP3A4, with some contribution from CYP2D6. Variations in CYP3A4 metabolism among patients can be substantial, leading to differences in drug

response. CYP3A4 can be induced by rifampicin and St. John's Wort, while erythromycin can inhibit its activity.

Following metabolization, oxycodone produces three pharmacologically active metabolites: noroxycodone, oxymorphone, and noroxymorphone. Although the analgesic effects of these metabolites are not well-understood, they are formed in minimal quantities, indicating that the parent drug is primarily responsible for the analgesic effect. CYP2D6, although subject to genetic variability, plays a minor role in oxycodone metabolism and has limited clinical significance.

The elimination half-life of oxycodone ranges from 2 to 5 hours, depending on the route of administration. Intravenous oxycodone exhibits a rapid onset of action, providing pain relief within approximately 5 to 8 minutes. Importantly, unlike morphine, oxycodone is less susceptible to efflux transporters like P-glycoprotein (P-gp), making its effect potentially more predictable in patients with compromised P-gp function, such as those with serious brain injuries [1].

Interestingly, our findings indicated that a higher number of boluses of oxycodone were required postoperatively to achieve similar pain control compared to piritramide. Despite the increased opioid usage, there was no notable increase in the recurrence of adverse events in the oxycodone group, and patient satisfaction levels were similar in both groups.

In contrast to Sebastian et al.[5] findings, where they reported a higher incidence of side effects, specifically nausea and vomiting, in the piritramide group compared to oxycodone, this trend was not observed in our study.

Several factors could potentially explain the higher opioid consumption in the oxycodone group. Since patients had a PCIA device, they had the autonomy to determine the number of boluses they received. It is conceivable that oxycodone may be more prone to addiction than piritramide, leading patients to request more boluses. More scientific work is needed to validate this conclusion.

Another possibility is that the doses used in our study were not equipotent. Patients received 2 mg of oxycodone per bolus or 3 mg of piritramide. Piritramide is a well-studied medication with a known morphine equivalent of approximately 2 mg morphine to 3 mg piritramide. A study by Silvasti et al. suggested equipotency between IV morphine and IV oxycodone [8], while another study by Lenz proposed that oxycodone was more potent than morphine for visceral pain relief [3]. In our study we used the same equianalgesic dose ratio (EDR) that Silvaste et al suggested; but we found that a higher dose of oxycodone was needed to achieve the same level of pain control. This is a contradictory finding in our study compared with previous studies and warrants further investigation.

One of the limitations of this study is that the investigators were not blinded. During the research process, only the patients were blinded. Another limitation of this study is the heterogeneity of surgical procedures and the involvement of different surgeons. Since the study included patients who underwent

different surgical techniques or were treated by various surgeons, there may have been variations in surgical skill, experience, and approach, potentially influencing the outcomes observed.

Overall, our study provides more insights into the effectiveness and safety of IV oxycodone compared to IV piritramide for postoperative pain management. Additional research is needed to explore the underlying factors causing differences in opioid consumption between the two groups. This includes optimizing dosing strategies and assessing the long-term outcomes and potential addictive properties of oxycodone in various surgical contexts.

Conclusion

In conclusion, the findings of this study indicate that intravenous oxycodone does not provide superior pain control compared to piritramide following abdominal and gynaecological operations. Interestingly, the oxycodone group demonstrated higher opioid usage and a greater need for boluses. Despite this, oxycodone was found to be a safe postoperative analgesic with low adverse events.

The reason for the increased opioid usage in the oxycodone group remains unclear. One possibility is a higher susceptibility to addiction associated with oxycodone use. Alternatively, it is plausible that the conversion ratio between intravenous oxycodone and intravenous piritramide was not equipotent, leading to differences in opioid requirements.

Further research is necessary to elucidate the underlying factors contributing to the higher opioid consumption observed in the oxycodone group. Investigating the potential addictive properties of oxycodone, as well as optimizing the dosing strategies and exploring the comparative efficacy of different opioids in this context, will be crucial areas for future investigation. Such studies will enhance our understanding of postoperative pain management and inform evidence-based practices for improved patient outcomes.

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Tables

Table 1

Activity	Screening (D-14 until D-1)	Day of surgery (D0)	First follow-up (D1)	Second follow-up (D1)
Assessment of Eligibility	x			
ICF	x			
Randomisation	x			
Demographic Information	x			
Medical History	x			
Prior and concomitant medication	x			
ASA score	x			
Physical Examination	x			
Haematology	x		x	
Vital Signs	x	x	x	x
Pain Evaluation		x	x	x
Side Effects		x	x	x
RASS		x	x	x
Satisfaction Score				x

Table 1: Overview of the study design.

Table 2

		oxycodone Group		piritramide Group			
		N	%	N	%	N	%
Type of surgery	Laparoscopic Abdominal surgery	21	56,8%	22	61,1%	43	58,9%
	Laparoscopic gynaecological surgery	9	24,3%	9	25,0%	18	24,7%
	Open Abdominal surgery	6	16,2%	4	11,1%	10	13,7%
	Open gynaecological surgery	1	2,7%	1	2,8%	2	2,7%
Total		37	100,0%	36	100,0%	73	100,0%

Table 2: Types of surgeries in the oxycodone and piritramide Group.

Table 3

	Group	N	Mean	Standard Deviation	Standard Error Mean
Total boluses received	oxycodone	37	17,32	12,925	2,125
	piritramide	36	11,47	8,286	1,381

Table 3: Total boluses received in the oxycodone vs. piritramide group.

Figures

Figure 1

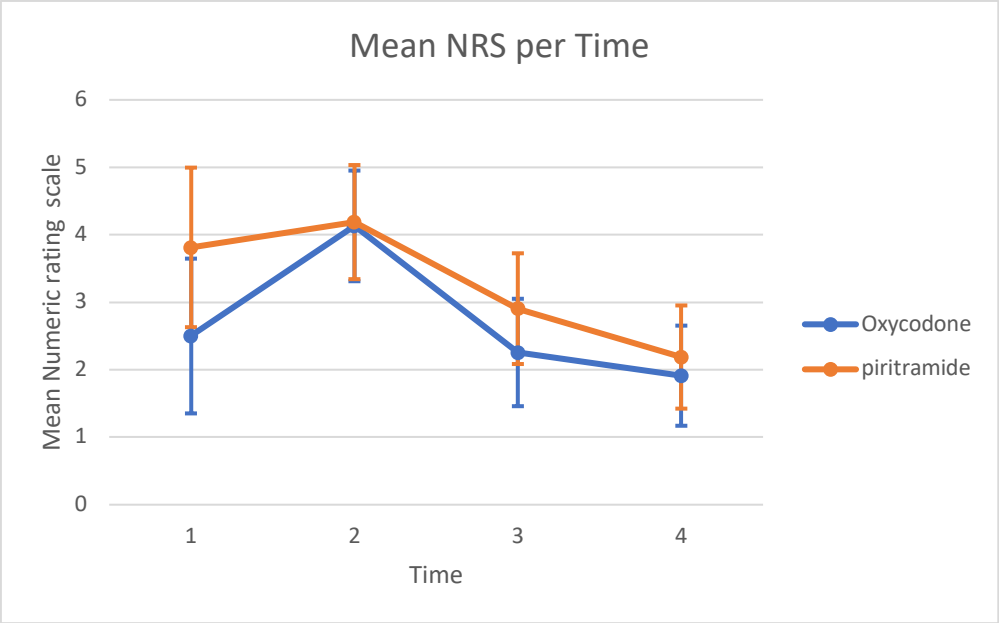

Figure 1: Mean Numeric Rating Scale (NRS) over time. Time 1 is pain scores in the Post-Anesthesia Care Unit (PACU) upon the patient's awakening, time 2 is one hour after awakening, time 3 is the Morning of Day 1and time 4 is the Evening of Day 1.

Oxycodone: Time 1 (2,5 Standard error (SE) 0,574), Time 2 (4,132 SE 0,410), Time 3 (4,132 SE 0,410), Time 4 (2,256 SE 0,398)

Piritramide: Time 1 (3,813 SE 0,592), Time 2 (4,188 SE 0,423), Time 3 (2,906 SE 0,411) Time 4 (2,188 SE 0,383)

Figure 2

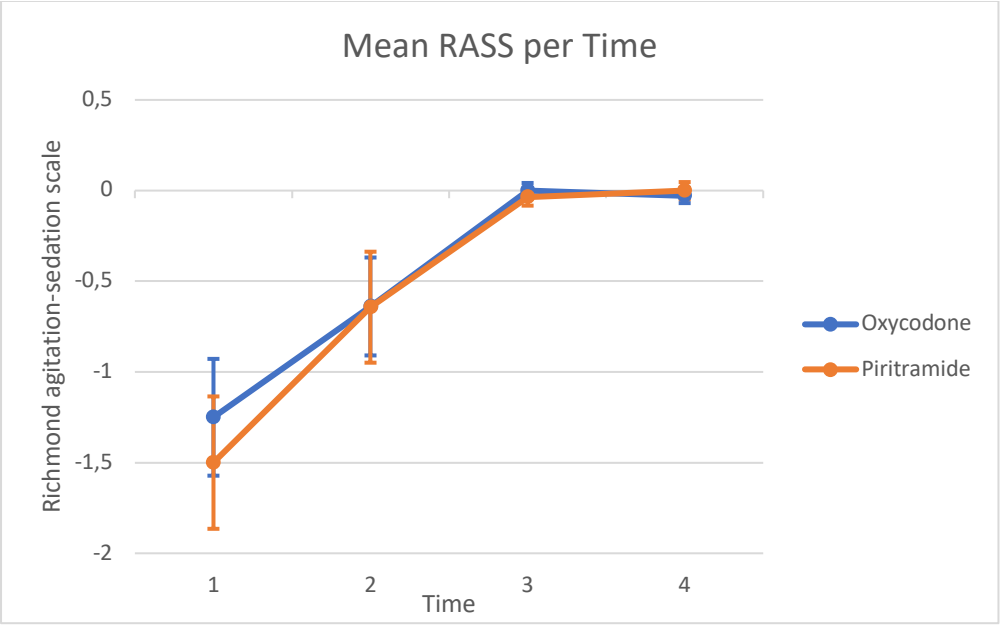

Figure 2: Richmond agitation-sedation scale (RASS) over time. Time 1 is RASS in the Post-Anesthesia Care Unit (PACU) upon the patient's awakening, time 2 is one hour after awakening, time 3 is the Morning of Day 1and time 4 is the Evening of Day 1.

Oxycodone: Time 1 (-1,25 Standard error (SE) 0,161), Time 2 (-0.639 SE 0,135), Time 3 (0 SE 0,021), Time 4 (-0,028 SE 0,021)

Piritramide: Time 1 (-1,5 SE 0,182), Time 2 (-0,643 SE 0,153), Time 3 (-0,036 SE 0,024), Time 4 (0 SE 0,024)