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ORIGINAL RESEARCH ORTHOPEDIC ANESTHESIA

Pre-emptive use of prolonged release oxycodone/naloxone combo significantly reduces postoperative pain after total hip arthroplasty

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ABSTRACT

Background & Objective: The role of pre-emptive analgesia remains controversial. Targeting the end of the surgery, the needed serum levels of analgesic can be achieved using prolonged release preparations, reducing acute postoperative pain and related complications. We assessed the efficacy of pre-emptive intake of prolonged release oxycodone/naloxone combination tablets on postoperative pain.

Methodology: We enrolled 152 patients who underwent an elective total hip arthroplasty under general anesthesia in the current study. The patients who prospectively received a tablet of prolonged release oxycodone 10 mg + naloxone 5 mg just before induction of general anesthesia, were categorized in the pre-emptive group (n = 76). The hospital records of 76 patients, already operated, and who did not receive any pre-emptive opioids before induction were included in the control group. Patients' postoperative pain was measured on the Numerical Rating Scale (NRS). Piritramide is routinely used in our hospital for postoperative pain titrated until NRS level of 3 or less is achieved. Study outcomes were; the dose of piritramide used, and the time spent in post anesthesia care unit (PACU).

Results: Preoperative use of oxycodone/naloxone combination reduces the frequency of postoperative opioid use (25% vs. 7.8%; P = 0.007) and the piritramide usage (12 mg vs. 15 mg; P = 0.001) in the pre-emptive group compared to the control group. The number of patients who needed relatively small doses of piritramide (≤ 9 mg piritramide) was more in the pre-emptive group compared to the control group (44.7% vs 25%; P = 0.017).

Conclusion: The pre-emptive use of oxycodone/naloxone combination is a safe and effective way to reduce postoperative pain after total hip arthroplasty.

Abbreviations: NRS - Numerical Rating Scale; PACU - Post Anesthesia Care Unit; BMI - Body Mass Index; NSAIDs - Non-Steroidal Anti-inflammatory Drugs

Key words: Analgesia, Pre-emptive; Oxycodone; Pain, Postoperative; Total Hip Arthroplasty

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1. INTRODUCTION

Early mobilization and optimal pain management take the central role in the context of 'Fast Track' surgery concept after total hip arthroplasty.[1] The essential precondition for the mobilization is a painless state. Pain management has to be continued in PACU, and even afterwards. There is always a possibility of transition from acute postoperative pain into chronic pain having a big socioeconomic impact and worsening patients' life quality. The exact pathophysiological mechanisms that are involved in the process of the transition are not known yet.[2] An optimal pain management in PACU can be an essential aspect of early mobilization and in preventing chronic pain.

The pre-emptive analgesia refers to using various analgesic methods before surgical incision or stimulation to change the perception of harmful stimulation by peripheral and central nervous systems and to reduce central sensitization, hyperalgesia, and touch-induced pain. Although postulated in the early 20th century,[3] and confirmed trough several animal studies, this concept is still controversial, and has not found a solid ground in clinical practice.[4–8] Several studies tested oral oxycodone as a pre-emptive medication. In one study oxycodone showed superiority in comparison to sufentanil,[9] but in another study oxycodone presented a negative impact on postoperative pain and postoperative mobilization after total joint arthroplasty.[10]

Targeting the end of the surgery, the needed level of analgesic in serum could be achieved using prolonged release tablets. Usage of opioids and opioid related complications (nausea, respiratory and airway complications) in PACU could be reduced. That way we could improve postoperative pain management and patient safety.

The goal of our study was to test an effect of pre-emptive application of oral prolonged release oxycodone/naloxone preparation in addition to routine intraoperative multimodal regime on pain relief after total hip arthroplasty.

2. METHODOLOGY

Ethics approval was issued by the Saxon State Chamber of Medicine, Dresden, Germany on 19.09.2022 (Number: EK-BR-109/22-1). All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Due to retrospective character of the study and the process of anonymization of the patient data, there was no need for formal consents of participation.

Patient selection

This retrospective study included all patients who received a general anesthesia for total hip arthroplasty in the Forrest Hospital in Bad Dueben between April 23, 2021 to February 01, 2022. In September 2021, we started pre-emptive medication and we used it as a starting point for recording data. We recorded data bidirectionally.

Patients were categorized following pre-emptive medication into 'pre-emptive group', in which patients received a tablet containing prolonged release oxycodone 10 mg and prolonged release naloxone 5 mg right before introducing general anesthesia with a sip of water ('pre-emptive group'). We selected the patient records of 76 patients operated upon during February 2021 to September 01, 2021, who did not receive any kind of pre-emptive analgesia ('standard group'). General anesthesia was performed individually and according to current guidelines. Overall doses of piritramide, sufentanil and overall time spent in PACU were compared. Patients with pre-existent opioid medication were excluded from the study.

Oxycodone is a widely prescribed oral opioid to treat severe pain. Oxycodone is a semi-synthetic opioid with an agonist activity on μ, κ and δ receptors. Equivalence with regard to morphine is 1:2.[11] In the Forest Hospital in Bad Dueben, we use oxycodone/naloxone combo for postoperative pain therapy as a standard for the first couple of days until full mobilization. The fixed combination with naloxone reduces bowel paralysis and obstipation without having any systemic effect by oral bioavailability of only three percent in patients without hepatic impairment.[12] The prolonged release form provides a constant blood level of oxycodone without any peaks resulting in respiratory complications or in airway obstruction. According to pharmacokinetics of oxycodone/naloxone the absorption is biphasic with first serum level peak of oxycodone approximately one hour after oral intake,[11] which correlates approximately with surgery time for total hip arthroplasty in our hospital.

Exactly these positive effects of prolonged release and time needed to achieve the analgesic threshold level in serum were reasons we choose oxycodone/naloxone combination for the pre-emptive medication. Our goal was, if possible, to avoid or to reduce to a minimum any intraoperative interaction of two opioids (sufentanil and oxycodone) and to achieve the analgesia threshold serum level of oxycodone at the end of the surgery and that way to reduce the consumption of piritramide and possibly time spent in PACU.

General anesthesia and PACU

All patients received standardized premedication with benzodiazepines. General anesthesia was performed

according to current guidelines using sufentanil, propofol, rocuronium and maintained using sevoflurane. All patients received one or more analgesics out of ibuprofen, metamizole, parecoxib, or Dexketoprofen, or clonidine or paracetamol. After the surgery all patients were shifted to the PACU. Piritramide 2−3 mg was injected IV with a gap of at least 10−15 min until we achieved the target analgesia level. The target analgesia level was measured with an 11-point numerical rating scale (NRS), where 0 meant 'no pain', and point 10 meant 'the worst possible pain'. The target was to keep the NRS score at 3 or less. Our patients were treated in the PACU until they were transferred to the orthopedic department, when fully awake, NRS ≤ 3, stable vital functions, no bleeding and oxygen saturation of 90% or more.

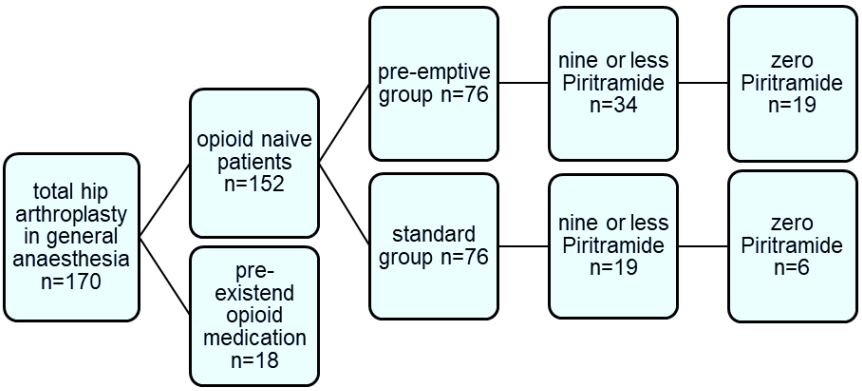

Figure 1: Patient flow diagram

Scanned anesthetic protocols and patients' medical records were used to collect and record data.

Statistical analysis

The results are presented as the median value (50% quartile) and the interquartile range (25%−75%), as well as the mean value and the standard deviation. Metric parameters were tested for the normality of their distributions using the Shapiro-Wilk test.

The results (age and height excluded) contradicted the assumption of a normal distribution. The differences between the groups were determined using the non-parametric Mann-Whitney U test. The results which did not contradict the assumption of normal distribution (age and height) were compared using T-test. Associated categorical parameters were tested using Fisher's exact test. The significance in Zero piritramide group and Nine or less piritramide group was determined using Fisher's exact test. Fisher's exact test was used as well testing the number of patients receiving NSAIDs, paracetamol and clonidine between standard and pre-emptive group. The alpha level of the study was P = 0.05. Consequently, significant test results were obtained at a P < 0.05. The analyses were performed using GraphPad Prism for Windows version 5.

3. RESULTS

In total, 152 patients met the inclusion criteria. According to the pre-emptive medication, the patients were divided into two groups: pre-emptive group (n = 76) and standard group (n = 76).

The pre-emptive group showed significantly lower consumption of piritramide compared to the standard group (12 mg vs. 15 mg; P = 0.001). Additionally, the number of patients who did not need any piritramide at all (zero-piritramide group) was significantly higher in the pre-emptive group (19 vs. 6; P= 0.007). Further, the number of patients who needed 9 mg or less piritramide (≤ 9 piritramide group) was significantly higher in pre-emptive group (34 vs.19; P = 0.017).

We found significantly higher intraoperative consumption of sufentanil in the pre-emptive group (40 µg vs. 35 µg; P = 0.018).

The median time in PACU until transfer to orthopedic department was shorter in the pre-emptive group, but we found no significant difference between the groups.

Several NSAIDs, paracetamol and clonidine were administered. There is a higher frequency of ibuprofen administration in the standard group; e.g., 60.52% vs. 78.94% (P = 0.022).

4. DISCUSSION

The main finding of this study was that the pre-emptive medication with oxycodone/naloxone combo significantly reduces the amount of piritramide that is needed to be administered to make the patients pain free (NRS of 3 or less) in the PACU. The dose of piritramide was more variable in the pre-emptive group showing greater interquartile range shifting the range towards the lower end. This effect is more recognizable when isolating only the patients that needed no or relatively mild dose of piritramide (nine milligrams or less).

Twenty five percent of the patients in the pre-emptive group did not need piritramide at all and approximately 45% of the patients needed only 9 mg or less piritramide

Table 1: Comparative demographic data of two groups

Parameter	Pre-emptive group (n = 76)	Standard group (n = 76)	P- value
Age (y)	68.72 ± 8.721	68.67 ± 8.599	0.971
ASA	2 (2−3)	2 (2−3)	0.123
Sex (male/female)	34/42	31/45	0.743
Weight (kg)	81 (73.25−93.75)	84 (69.25−99.75)	0.937
Height (m)	1.695 ± 0.089	1.689 ± 0.089	0.654
BMI (kg/m²)	28.7 (25.83−32.2)	28.8 (25.73−32.35)	0.987

Data are presented as median (IQR), mean ± SD (standard deviation) or numbers, ASA (American Society of Anesthesiologists), BMI (Body Mass Index)

Table 2: The effect of oxycodone/naloxone

Parameter	Pre-emptive group (n = 76)	Standard group (n = 76)	P- value
Piritramide dose (mg)	12 (1.5−15)	15 (9.25−15)	**0.001**
Zero-piritramide	19 (25)	6 (7.89)	**0.007**
Nine or less piritramide	34 (44.7)	19 (25)	**0.017**
Sufentanil dose (µg)	40 (30.63−40)	35 (30−40)	**0.018**
Ibuprofen (400 mg−600 mg)	46 (60.52)	60 (78.94)	**0.022**
PACU stay (min)	165 (140−203.8)	192.5 (137.5−225)	0.175
Clonidine (75 µg−150 µg)	14 (18.42)	6 (7.8)	0.092
Paracetamol (0.5 g−1 g)	44 (57.89)	40 (52.63)	0.624
Parecoxib (40 mg)	23 (30.26)	26 (34.21)	0.728
Metamizole (1g−2 g)	70 (92.10)	69 (90.78)	1.000
Dexketoprofen (50 mg)	3 (3.9)	1 (1.3)	0.620
Pethidine (12.5 mg−25 mg)	1 (1.3)	2 (2.6)	1.000

Data are presented as median (IQR), number and number (percentage), PACU (Post Anesthesia Care Unit), T (Time)

to become pain free. This is in contrast with 8% and 25% in the standard group. We, therefore, found this effect to be substantial, affecting nearly half of the patients.

We used a prolonged release oxycodone 10 mg / naloxone 5 mg tablets, regardless of the patient weight and comorbidity, as this combination is readily available and convenient to use. A minimal starting dose of oxycodone/naloxone was used in anticipation of possible side effects and possible interaction with ongoing general anesthesia. A more aggressive approach could have had a more profound effect on reduction of piritramide dose, increasing the number of patients that needed no piritramide at all.

The patients in the pre-emptive group showed a shorter median time spent in the PACU, but without statistical significance. Although the most important factors, the postoperative pain and clinical state of the patients are not the only factors that influence the patient stay and transfer schedule from PACU. Due to shortage of medical personnel and time-consuming shift changes, the time intervals in PACU are often prolonged. That could explain the lack of statistical significance. On the other hand, a relatively long stay in PACU provided us a good feedback on our pain management. In fact, this could be considered as an additional strength of the study, because we demonstrated the ability to maintain a painless state for a long period of time.

There is also a significantly higher median sufentanil dose used during anesthesia in the pre-emptive group (P = 0.018), which may indicate that the interaction between

sufentanil and naloxone may have weakened the effect of sufentanil. Although a low naloxone bioavailability of only 3% and very strong hepatic first pass metabolism make naloxone effect irrelevant on systemic analgesia, one recent study showed that the hepatic first-pass effect on naloxone could be weakened in patients with hepatic impairment.[12] It is possible that some of our patients have had some unrecognized hepatic impairment. These possible interactions could be one of the reasons for higher intraoperative consumption of sufentanil. However, there was no recorded awareness or any kind of exorbitant usage of opioids or anesthesia gas.

We did not use any standardized dosing schema of sufentanil. Initial dose of sufentanil was administrated individually according to patients' weight, age and comorbidity and the next doses during anesthesia were repeated with the pulse and blood pressure changes. This can be a factor of limitation for assessment and comparison of the median values of sufentanil.

The context sensitive half-life of sufentanil is linear,[13] and even comparable with remifentanil in time to extubation trial.[14] Therefore, it is unlikely that higher intraoperative sufentanil dose in the pre-emptive group influenced the usage of piritramide in PACU considering rather small difference of only 5 µg in the median comparing to standard group and rather long time spent in PACU (several hours). We find that although statistically significant, the difference in dosage of sufentanil between groups is not of clinical relevance.

The lack of standardized dosage of anesthetics is also the reason we have not recorded and compared time to extubation between the groups. However, we did not record any unusual prolonged time to extubation by any of our patients.

There were no case of aspiration, so we can confirm that the peroral administration of oxycodone/naloxone tablets just before introducing general anesthesia is a safe procedure.

There was not any difference in frequency of clonidine administration between groups, therefore we can conclude that clonidine did not affect the amount of piritramide to achieve the desired level of analgesia.

We found a higher frequency of ibuprofen administration in the standard group. However, the administration of NSAID was not standardized. All of the patients received some NSAIDs or paracetamol at the end of the surgery and the majority of patients received some NSAID or paracetamol in the PACU. It was left to the anesthesiologist to select the preferred drug and the dose. Therefore, despite the apparent statistical significance, we cannot conclude that the pre-emptive medication with oxycodone/naloxone reduced the frequency of ibuprofen administration in the PACU.

The pain assessment after surgery is a challenging task. To conform with a recent guideline, we use NRS as one of the recommended scales to assess the postoperative pain.[15] The pain scale 3 or less is accepted as a painless state. We found high compliance in using NRS among nurses and patients and had positive feedback.

A standard scoring system is used to transfer the patients from our PACU, including SpO_2 90% or more, NRS 3 or less, stable vital signs and no bleeding. That way we quantified our treatment in PACU as objectively as possible and achieved an optimal individual care for each of our patients. This can also be considered a strength of the study.

5. LIMITATIONS

Even though our sample of patients undergoing elective total hip arthroplasty is relatively large in size, a retrospective study cannot be fully standardized, and always has multiple points of differences in the data available, including the choice of different drugs and their doses used and the time to use in these patients.

6. CONCLUSION

We conclude that the pre-emptive medication with oxycodone 10 mg plus naloxone 5 mg significantly reduces pain in PACU after total hip arthroplasty, compared with a standard premedication with no analgesic. It is a safe, fast and effective way to reduce postoperative pain.

7. Data availability

The data generated during this research is available with the authors.

8. Conflict of interest

The authors declare no conflict of interest, and no external or industry funding was involved.

9. Authors contributions

Jovan Jocović and Milena Jocović contributed to the work equally and should be regarded as co-first authors. All authors took part in collection of data, statistical analysis and drafting the paper. All authors have read and endorse the manuscript

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