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Pain Control and Opioid Consumption in Patients Undergoing Total Hip or Knee Arthroplasty Receiving a Preoperative Low Dose of Gabapentin

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Abstract: Background: Meta-analyses and randomized controlled trials were inconclusive regarding the role of gabapentinoids in patients undergoing joint arthroplasties. The aim of the present study was to investigate the effect of a preoperative low dose of gabapentin in patients undergoing total hip (THA) and knee arthroplasties (TKA). Methods: A retrospective observational study was conducted on 135 patients undergoing THA and TKA at the National Orthopedic Hospital Cappagh, Dublin, from July to December 2022. The primary outcome was the assessment of numerical rating scores (NRS) for postoperative pain at various time intervals. Results: During the observation period, 55 patients received a preoperative dose of gabapentin, while 80 patients did not. Statistically significant differences in numerical rating scores (NRS) were found at 6 (3 vs. 0, $p < 0.001$), 12 (4 vs. 2, $p < 0.001$), 18 (4 vs. 3, $p < 0.001$), and 24 h (4 vs. 3, $p = 0.010$) after surgery, in favor of the group receiving gabapentin. A reduction in opioid consumption, measured as morphine equivalents, was also noted in the gabapentin group (40 vs. 30 mg, $p = 0.040$). Conclusions: A low preoperative dose of gabapentin was associated with reduced postoperative pain and opioid consumption in patients undergoing TKA and THA, without impacting hospital stay. Prospectively designed trials are encouraged to assess the safety and effect on pain control of a preoperative low dose of gabapentin.

Keywords: gabapentin; total hip arthroplasties; total knee arthroplasties; chronic pain

Citation: Fioccola, A.; Pinto, A.M.; Nolan, R.; Free, R.; Tariq, W.; Pozzi, T.; Villa, G.; Di Filippo, A.; Romagnoli, S.; Tujjar, O. Pain Control and Opioid Consumption in Patients Undergoing Total Hip or Knee Arthroplasty Receiving a Preoperative Low Dose of Gabapentin. *Anesth. Res.* **2024**, *1*, 180–192. https://doi.org/10.3390/anesthres1030017

Academic Editors: Luk Hsiang Ning and Bruce D. Spiess

Received: 23 June 2024
Revised: 16 August 2024
Accepted: 14 September 2024
Published: 11 November 2024

1. Introduction

Postoperative pain management in patients undergoing total hip and total knee arthroplasties (THA, TKA) can be challenging. The use of peripheral nerve blocks as an adjunct to subarachnoid techniques may be associated with decreased postoperative opioid consumption and faster postoperative mobilization [1–3]. A major concern with locoregional techniques is the potential increased risk of falls due to residual motor blockade, as demonstrated after femoral nerve blockade [4–6] and with other locoregional techniques [7,8]. Due to the complex innervation of the hip and knee [9,10], there is no consensus in the literature on the best management for THA or TKA. A recent Cochrane review, which included data from 2491 patients undergoing total hip arthroplasty, showed no effect of peripheral nerve blocks compared with a subarachnoid technique alone in postoperative pain management [11]. Additional heterogeneity in the field of locoregional anesthesia is

introduced by variability in patients and surgical techniques [12,13], making the individualization of the technique essential.

Gabapentinoids (pregabalin, gabapentin) are drugs typically used for patients with chronic neuropathic pain and epilepsy, showing the ability to reduce seizure frequency in this population [14–16]. Their mechanism of action involves the inhibition of calcium influx and subsequent release of excitatory neurotransmitters with different pharmacodynamic and pharmacokinetic properties [16]. Their high water solubility grants them excellent oral bioavailability. Large Amino Acid Transporters (LAT), particularly LAT1, are primarily responsible for their absorption [17]. LAT1 is the main transporter responsible for gabapentin absorption, while pregabalin's absorption is also mediated by additional pathways, which give it a higher potential for oral absorption compared to gabapentin and a linear increase in plasma concentration with higher oral doses [18]. Gabapentin's oral bioavailability ranges from 27% to 80%, being inversely proportional to the total dose administered [19]. Pregabalin's oral bioavailability exceeds 90%, regardless of the dosage administered [20]. The maximum rate of pregabalin absorption is about three times higher than that of gabapentin, with peak blood concentrations reached in one hour [20]. Gabapentin reaches its peak three hours after oral administration [21]. These molecules undergo negligible metabolism and are primarily eliminated by the kidneys [20]. After a single oral dose, gabapentin and pregabalin have a similar half-life, ranging from 5 to 7 h. They can reach steady-state concentrations after 24–48 h of repeated administration [22]. Dizziness, sedation, dry mouth, and blurred vision are the most frequent side effects of these drugs in patients without comorbidities. Concomitant administration with opioids and their administration on the day of surgery significantly increase the risk of respiratory depression, as recently reported [23]. In patients undergoing THA and TKA, the risk of respiratory depression was shown to be increased in those who received a gabapentinoid on the day of surgery, with the risk being dose-dependent [24].

Beyond their conventional clinical uses, gabapentinoids are often advocated in the perioperative setting as adjunct therapy to enhance pain relief and decrease opioid consumption [25,26], along with their relative side effects [27]. Several meta-analyses have been conducted to investigate the effect of preoperative gabapentinoid administration on postoperative pain control and opioid consumption in patients undergoing TKA or THA in different contexts, yielding conflicting results [27–32]. Among the main concerns regarding the use of gabapentinoids in the perioperative setting are the risks of sedation and respiratory depression [27], which might limit their use in this clinical context. The results of these meta-analyses do not provide definitive evidence on the utility of perioperative gabapentin administration in patients undergoing THA or TKA. In this study, we aimed to assess whether a single, low-dose preoperative administration of gabapentin was associated with better postoperative pain control in patients undergoing elective THA and TKA. Additionally, we sought to determine whether gabapentin had any effect on postoperative opioid consumption, length of hospital stay (LOS), and length of stay in the post-anesthesia care unit (PACU).

2. Materials and Methods

2.1. Study Design and Population

We conducted a retrospective observational study on adult patients undergoing total hip or total knee arthroplasty at the National Orthopedic Hospital Cappagh, Dublin. The exclusion criteria were as follows: age under 18 years, pregnancy, THA or TKA revision, bilateral THA or TKA, history of chronic pain, diabetes-associated polyneuropathy, ongoing domestic therapy with gabapentinoids, and an American Society of Anesthesiologists (ASA) score of 4 or 5 at the preoperative evaluation.

One hour before surgery, patients received or did not receive an oral dose of gabapentin based on the anesthesiologist's prescription. They subsequently underwent either a subarachnoid block (with or without sedation) or general anesthesia. The observation period

spanned from 1 July 2022 to 31 December 2022. The study was approved by the Local Ethics Committee (NOHC-2022-ETH-DC-CEO-339).

2.2. Sample Size Calculation

Liszka et al. [33] evaluated the analgesic effect of a single preoperative dose of oral gabapentin (300 mg) in elderly patients undergoing total knee arthroplasty. Twenty-four hours after surgery, they found a Numerical Rating Scale (NRS) score of 2.00 versus 2.80 in patients who received gabapentin compared to those who did not. To demonstrate a similar difference in our study between the two groups, considering a similar pooled standard deviation (1.5) [33], with a power of 0.8 and an alpha of 0.05, a sample size of 55 patients per group was needed. The calculations were based on a two-sided *t*-test.

2.3. Data Collection

For the present study, we collected pain scores at 30 min, 6, 12, 18, 24, and 48 h after surgery. These time points correspond to the routine postoperative evaluations performed by nurses at our center. When administered, gabapentin was given as a low preoperative dose (300 mg), as routinely prescribed by physicians at our institution.

We also collected data on hospital length of stay (LOS), postoperative opioid consumption, and the duration of sensory and motor block in patients undergoing either subarachnoid block with sedation or general anesthesia.

2.4. Peripheral Pain Blocks

Preoperative peripheral nerve blocks were performed based on the anesthesiologist's discretion. In the present study, a lateral femoral cutaneous nerve (LFCN) block or a fascia iliaca block was performed in patients undergoing THA. A fascia iliaca block, an adductor canal block, or an interspace between the popliteal artery and capsule of the knee (iPACK) block was performed in patients undergoing TKA.

2.5. Intraoperative Monitoring

Intraoperative monitoring data were extracted from the anesthesiologist's chart. We recorded the lowest peripheral oxygen saturation (SpO_2) and the lowest mean arterial pressure (MAP) observed during surgery, any conversions to general anesthesia, as well as the average propofol effector site concentration (C_{et}).

2.6. Postoperative Pain Medications

At our center, the postoperative pain management regimen for patients undergoing THA/TKA was standardized and included paracetamol (1000 mg every 6 h), ibuprofen (5–10 mg/kg every 8 h), and an opioid (oral morphine or oxycodone) as needed when the NRS was equal to or greater than 3, despite the administration of paracetamol and ibuprofen. Non-steroidal anti-inflammatory drugs (NSAIDs) were typically avoided in patients with chronic kidney disease (CKD).

2.7. Numerical Rating Score

The Numerical Rating Score (NRS) is a widely used pain assessment tool that evaluates pain severity on a scale of 0 to 10, where 0 indicates "no pain" and 10 signifies "the worst pain imaginable". In many clinical settings, these scores are documented in the patient's medical record, enabling clinicians and researchers to monitor pain intensity over time. At our center, NRS scores were collected in the PACU immediately after surgery, 30 min postoperatively, and again before the patient's discharge. Subsequently, on the clinical ward, NRS scores were collected every 3 h during routine nursing activities.

2.8. Morphine Equivalent Dose Calculation

To standardize and quantify the amount of opioid administered postoperatively, we calculated morphine equivalent doses using the opioid conversion calculator from the Oregon

Pain Guidance website (OPG, https://www.oregonpainguidance.org/opioidmedcalculator/, accessed on 15 august 2024).

2.9. Statistical Analysis

Continuous data were expressed as median [interquartile range], while categorical data were expressed as number (%). The normality of the distribution of continuous variables was assessed using the Shapiro-Wilk test. Discrepancies in percentages between groups were assessed using the chi-squared test, while differences between continuous variables were assessed using the Student's *t*-test or the Wilcoxon-Mann-Whitney U test, as appropriate. To investigate the differences in NRS between groups (patients who received and did not receive gabapentin) across the measurement time points, we used a two-way analysis of variance (ANOVA), with groups as a fixed between-subjects effect and time as a fixed within-subjects effect; a post-hoc test was performed using the Student's *t*-test, as appropriate. We performed multiple linear regressions to adjust the effect of group on NRS (at each time point) and on administered morphine equivalents for potential confounders, namely patients' comorbidities. To further confirm the results of this latter analysis, a linear mixed model was used to study the longitudinal time course of NRS in the two groups of patients (receiving and not receiving a preoperative dose of gabapentin). A p-value < 0.05 was considered statistically significant. All analyses were performed using RStudio (R Core Team, 2022; R Foundation for Statistical Computing, Vienna, Austria, version 2024.04.0+735).

3. Results

3.1. Patients' Enrolling

In Figure 1, we present a flowchart detailing the patient enrollment process. During the observation period, a total of 151 patients undergoing THA or TKA were enrolled. Sixteen patients were excluded due to the presence of one or more exclusion criteria. Among them, six patients had chronic pain, four patients underwent a TKA revision, three patients underwent a THA revision, and three patients had diabetes-associated polyneuropathy. As a result, 135 patients were included in the analysis. Of these, 55 received a preoperative dose of gabapentin (RG patients), as required by the sample size calculation, while the remaining 80 patients did not receive a preoperative dose of gabapentin (NRG patients).

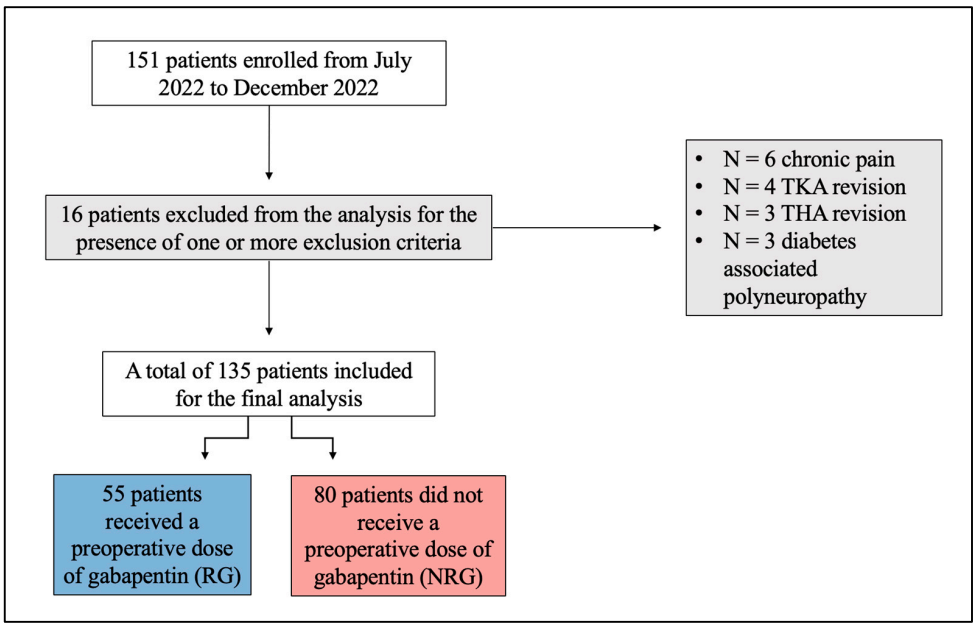

Figure 1. Study flowchart. Legends: TKA = Total Knee Replacement; THA = Total Hip Replacement; RG = Receiving Gabapentin group; NRG = Non-Receiving Gabapentin group.

3.2. Baseline Characteristics of the Study Population

In Table 1, we present the baseline characteristics of the study population according to the assigned group. As shown, the two groups were balanced in terms of anthropometric variables. In the RG group, there was a higher percentage of patients with chronic hypertension (57.5% vs. 72.7%, $p < 0.001$), a past medical history of cardiac ischemia, CKD (8.75% vs. 14.5%, $p = 0.004$), and one or more previous surgeries, whereas NRG patients were more likely to suffer from respiratory diseases, specifically chronic obstructive pulmonary disease (COPD) (10% vs. 3.6%, $p < 0.001$) and obstructive sleep apnea syndrome (OSAS) (10% vs. 5.4%, $p = 0.02$) (see Table 1 for details).

Table 1. Baseline patients' characteristics of the two study populations.

	NRG ***n* = 80**	**RG** ***n* = 55**	***p***
THA, *n* (%)	35 (43.7)	25 (45.4)	
TKA, *n* (%)	45 (56.3)	30 (54.6)	
Female sex, *n* (%)	41 (51.2)	26 (70.9)	
Age, years	66.5 (59–73)	65 (60.5–73.5)	0.914
Weight, kg	86 (73.8–94.2)	88 (77–96.5)	0.217
Height, cm	165 (160–176)	168 (158–178)	0.816
BMI, kg/m^2	29.8 (26.8–34.1)	30.6 (27.6–34.8)	0.233
ASA score	2 (2–3)	2 (2–3)	0.640
Comorbidities			
Hypertension, *n* (%)	46 (57.5)	40 (72.7)	**<0.001**
Diabetes, *n* (%)	11 (13.75)	8 (14.5)	0.809
Cardiac valve disease, *n* (%)	4 (5)	1 (1.8)	**0.022**
Previous cardiac ischemia, *n* (%)	0 (0)	1 (1.8)	**0.004**
Cardiac arrhytmia, *n* (%)	6 (7.5)	6 (10.9)	0.100
COPD, *n* (%)	8 (10.0)	2 (3.6)	**<0.001**
Asthma, *n* (%)	11 (13.8)	6 (10.9)	0.230
OSAS, *n* (%)	8 (10.0)	3 (5.4)	0.021
CKD, *n* (%)	7 (8.8)	8 (14.5)	**0.007**
Neurological diseases, *n* (%)	7 (8.8)	4 (7.3)	0.490
Autoimmune diseases, *n* (%)	3 (3.8)	0 (0)	**<0.001**
Previous POD, *n* (%)	1 (1.2)	0 (0)	0.070
Allergies, *n* (%)	9 (11.2)	3 (5.4)	**0.003**
Previous surgery, *n* (%)	63 (78.7)	47 (85.4)	0.450

NRG = Non-Receiving Gabapentin group; RG = Receiving Gabapentin group; *n* = number; THA = total hip arthroplasty; TKA = total knee arthroplasty; BMI = body mass index; ASA = America Society of Anesthesiology; COPD = Chronic Obstructive Pulmonary Disease; POD = Postoperative Delirium. $p < 0.05$ are indicated as bold values.

3.3. Intraoperative Variables

In Table 2, we report intraoperative variables in the two groups. Surgery duration was longer in NRG patients (80 vs. 72 min, $p = 0.02$), while there was a higher percentage of general anesthesia (GA) conversion in RG patients (1.2% vs. 3.6%, $p = 0.02$). No significant differences were observed in paracetamol (18.8% vs. 30.9%, $p = 0.151$) and NSAID administration (21.2% vs. 12.7%, $p = 0.303$) during the surgery. The total surgical time was only slightly longer in the NRG group (80 min vs. 72 min, $p = 0.02$). The percentage of peripheral blocks was low and similar in the two groups (16.2% vs. 20.0%, $p = 0.199$), as was the total amount of periarticular anesthesia used (150 mL vs. 150 mL, $p = 0.998$). No differences were observed in the amount of sedation employed, lowest SpO_2, and lowest MAP recorded during the surgery. Three patients were converted to general anesthesia: one in the NRG group and two in the RG group. Interestingly, the administration of gabapentin was not associated with a longer postoperative length of stay in the PACU (33.5 vs. 30 min, $p = 0.2$).

Table 2. Intra-operative variables.

	NRG ***n* = 80**	**RG** ***n* = 55**	***p***
Gabapentin dose, mg	0 (0–0)	300 (300–300)	**<0.001**
Gabapentin dose pro-kg, mg/kg	0 (0–0)	3.45 (3.14–4.03)	**<0.001**
Paracetamol administration, *n* (%)	15 (18.8)	17 (30.9)	0.151
NSAID administration, *n* (%)	17 (21.2)	7 (12.7)	0.303
Total surgical time, min	80 (60–96)	72 (55–90)	**0.020**
Peripheral block, *n* (%)	13 (16.2)	11 (20.0)	0.199
Periarticular anesthesia, mL	150 (0–150)	150 (0–150)	0.998
Intra-operative sedation, *n* (%)	80 (100)	55 (100)	0.995
Average Propofol effector site concentration (μg/mL)	1.0 (0.8–1.3)	1.0 (0.7–1.2)	0.172
Lowest SpO_2, %	97 (96–98)	97 (96–98)	0.501
Lowest MAP, mmHg	64 (59–70)	64 (63–68)	0.467
Conversion to general anesthesia, *n* (%)	1 (1.2)	2 (3.6)	**0.023**
Time in PACU, min	33 (25–40)	30 (25–40)	0.200

NRG = Non-Receiving Gabapentin group; RG = Receiving Gabapentin group; NSAID = non steroidal anti inflammatory drug; SpO_2 = peripheral oxygen saturation; MAP = mean arterial pressure; PACU = post-anesthesia care unit. $p < 0.05$ are indicated as bold values.

3.4. Postoperative Pain Control

Postoperative variables in the two groups are summarized in Table 3. As shown, NRS was significantly higher in the NRG group at 6 h (3 vs. 0, $p < 0.001$), 12 h (4 vs. 2, $p < 0.001$), 18 h (4 vs. 3, $p < 0.001$), and 24 h (4 vs. 3, $p = 0.010$) after surgery. No differences were found at the end of surgery (0 vs. 0, $p = 0.990$), 30 min after (0 vs. 0, $p = 0.721$), and 48 h after surgery (2 vs. 2, $p = 0.992$).

Table 3. Postoperative variables.

	NRG ***n* = 80**	**RG** ***n* = 55**	***p***
NRS			
End of surgery	0 (0–0)	0 (0–0)	0.990
After 30 min	0 (0–0)	0 (0–0)	0.721
After 6 h	3 (1–4.2)	0 (0–2)	<0.001
After 12 h	4 (3.7–5.2)	2 (1–3.5)	<0.001
After 18 h	4 (3–5)	3 (0–4.5)	<0.001
After 24 h	4 (3–5)	3 (1–4)	0.010
After 48 h	2 (1–4)	2 (0–4)	0.992
Time to motor, min	300 (270–360)	300 (265–360)	0.821
Time to sensory, min	370 (320–420)	365 (310–480)	0.669
PONV, *n* (%)	20 (25)	11 (20)	0.097
Anti-emetic dose, mg	1 (0–2)	1 (0–1.5)	0.155
Paracetamol cumulative dose, g	8 (7–8)	8 (7–8)	0.170
Ibuprofen cumulative dose, g	2.4 (2.0–2.5)	2.4 (1.6–2.4)	0.103
Use of rescue opioid at day 1, *n* (%)	80 (100)	53 (96.4)	**<0.001**
Morphine equivalents, mg	40 (25–55)	30 (20–45)	**0.040**
Rehab impairment by pain, %	19 (23.8)	12 (21.8)	0.543
Hospital length of stay, hours	55 (48–70)	60 (48–72)	0.512

NRG = Non-Receiving Gabapentin group; RG = Receiving Gabapentin group; NRS = Numerical Rating Score; PONV = Post Operative Nausea and Vomiting. $p < 0.05$ are indicated as bold values.

Figure 2 summarizes data on postoperative pain scores, expressed as NRS. As shown, no statistically significant difference was observed immediately, 30 min, and 48 h after surgery, whilst lower pain scores were found in the RG group at 6 h, 12 h, 18 h, and 24 h after the surgery.

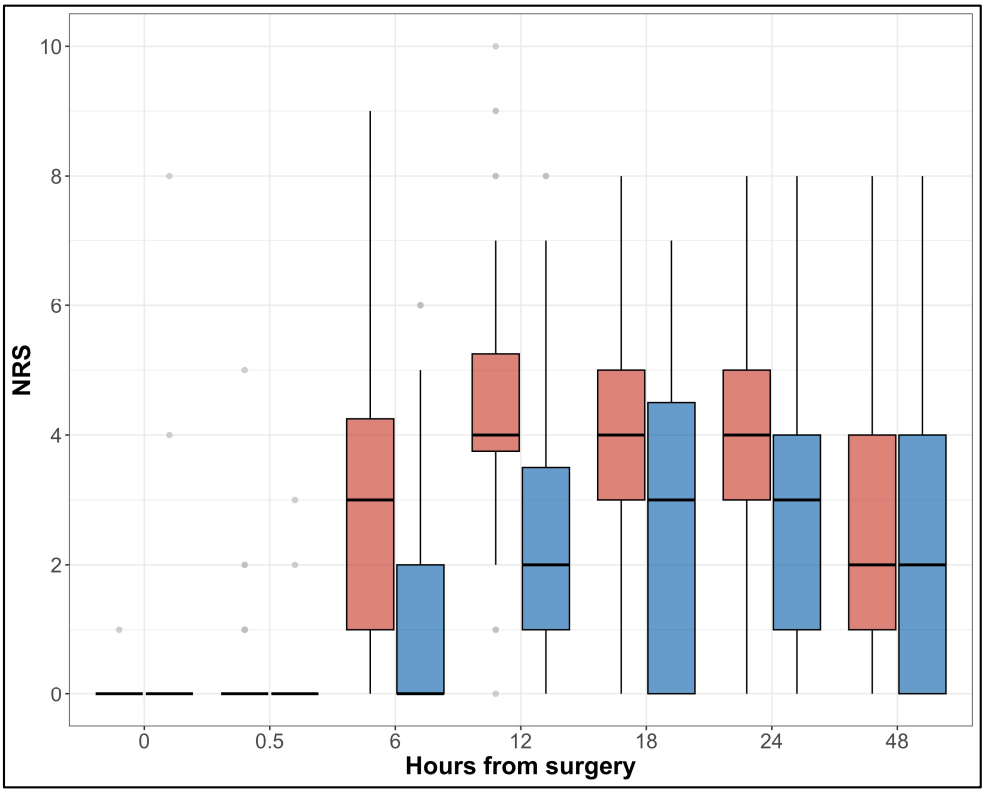

Figure 2. Mean and interquartile range of postoperative NRS in no-gabapentin (red boxplots) and gabapentin group (blue boxplots). Outliers are shown in gray. NRS: Numerical Rating Score. NRG: Non-Receiving Gabapentin group.

In Table S1, we show the results of the ANOVA test for the interaction of a preoperative dose of gabapentin and time on postoperative pain control, expressed as NRS. We found a significant interaction at 6 h (β = −1.77, $p < 0.001$), 12 h (β = −2.20, $p < 0.001$), 18 h (β = −1.70, $p < 0.001$), and 24 h (β = −1.22, $p < 0.001$) after surgery, consistent with the findings of the Wilcoxon-Mann-Whitney U test.

3.5. Postoperative Course of Other Key Variables

The time to motor recovery (300 vs. 300 min, $p = 0.821$) and time to sensory recovery (370 vs. 365 min, $p = 0.669$) after spinal anesthesia were similar in the two groups. No significant difference was observed in the cumulative postoperative dose of paracetamol (8 vs. 8 g, $p = 0.170$) and ibuprofen (2.4 vs. 2.4 g, $p = 0.103$) administered in the ward. No association was found between gabapentin administration and hospital length of stay (55 vs. 60 h, $p = 0.512$). The incidence of postoperative nausea and vomiting (PONV) was similar between the two groups, with a slightly higher trend in the NRG group (25% vs. 20%, $p = 0.09$). Conversely, patients who received a preoperative dose of gabapentin had a significantly lower request for rescue opioids on day 1 (80% vs. 53%, $p < 0.001$) and lower cumulative opioid administration during hospitalization, measured in morphine equivalents (30 mg vs. 40 mg, $p = 0.04$, Figure 3).

No adverse events, defined as respiratory depression or excessive sedation requiring respiratory support, were recorded.

In Table S2, we present the results of the multivariable linear regression performed to adjust for possible confounders in the outcomes, focusing primarily on the variables that differed between the two groups at baseline. As shown, the only factor associated with a lower NRS at 6 (ß = −1.71; $p < 0.001$), 12 (ß = −2.01; $p < 0.001$), 18 (ß = −1.63; $p < 0.001$), and 24 h (ß = −0.92; $p = 0.007$) was gabapentin administration. No effect of patients' comorbidities was shown to be associated with the outcome.

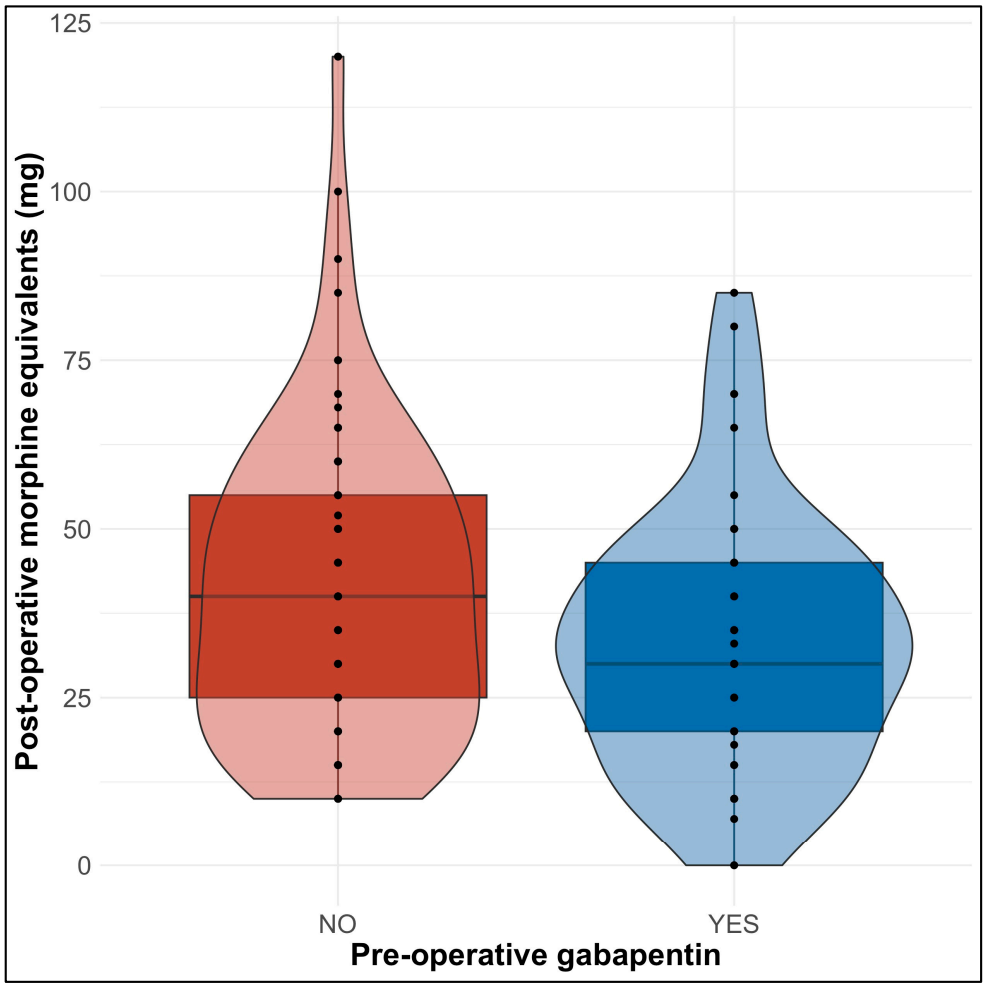

Figure 3. Boxplot and superimposed violin plots representing the overall postoperative opioid consumption in the group receiving a preoperative dose of gabapentin (blue) and not receiving a preoperative dose of gabapentin (red).

4. Discussion

Despite a consistent amount of available literature, randomized controlled trials and meta-analyses have failed to unambiguously define the role of gabapentinoid administration in the preoperative setting, showing conflicting results [27–32] (see Table 4).

Additionally, no significant difference has been observed in terms of postoperative pain control and opioid consumption when comparing a low versus a high preoperative dose of gabapentinoids [33]. The trials included in these meta-analyses are heterogeneous in terms of doses and patterns of gabapentinoid administration. Joshi et al. have already highlighted this and other major issues concerning these meta-analyses, thereby questioning their findings on the use of gabapentinoids in patients undergoing THA or TKA [34]. The quality of the studies included in these meta-analyses is sometimes questionable, particularly due to the lack of standardization regarding the use of co-analgesics, such as NSAIDs and paracetamol. Standardization is a critical factor in evaluating postoperative pain control in the perioperative setting due to the presence of multiple potential confounders and sources of background noise. In light of these considerations, Joshi et al. concluded that the applicability of the results from these meta-analyses is limited because it is difficult to standardize the settings in which the effects of gabapentinoids are tested [34]. Afterwards, encouraging results have come from the meta-analysis by Han et al., which showed a reduction in postoperative opioid consumption in patients treated with preoperative gabapentin in a meta-analysis involving 6 studies and more than 800 patients [31], thereby maintaining

interest in this class of drugs and their use in joint surgery. As frequently discussed in these studies, skepticism about the use of gabapentinoids includes the potential risk of sedation and respiratory depression when patients are discharged to the ward or, even more concerning, at home.

Table 4. Meta-analyses considering the association between gabapentinoids and postoperative pain control or opioid consumption.

Study	Gabapentin		Pregabalin	
First Author (Year of Publication)	**Pain Control**	**Opioid Consumption**	**Pain Control**	**Opioid Consumption**
Hamilton (2016) [27]	✗	✗	✓	✓
Zhai (2016) [28]	✓	✓	-	-
Dong (2016) [29]	-	-	✓	✓
Li (2017) [30]	-	-	✓	✓
Han (2017) [31]	✗	✓	-	-
Hannon (2020) [32]	✗	✗	-	✓

The meta-analyses concerning the role of gabapentinoids in postoperative pain control in different clinical settings were synthesized in this table. In the first column, the first author of the meta-analysis is reported. Full information about the specific study can be found in the reference list. Green ticks have been used to highlight studies in which gabapentinoids (gabapentin, second and third columns; pregabalin, third and fourth columns) were associated with the outcome (postoperative pain control and opioid consumption, as specified in the second row). Red crosses were used to synthesize studies in which gabapentinoids were not associated with better postoperative pain control or less opioid consumption. When no evidence was available, a black dash was used.

In our study, a preoperative low dose of gabapentin was administered to patients undergoing THA or TKA. The decision to administer the preoperative dose of gabapentin was not based on objective criteria, which poses a limitation to our analysis. However, this feature may help to describe prescribing patterns. Indeed, patients with hypertension, cardiac ischemia, and CKD were more likely to receive gabapentin, probably to achieve better perioperative analgesia and reduce opioid usage. Conversely, patients with respiratory conditions such as COPD and OSAS were less likely to receive gabapentin. The impact of these imbalances in the two study groups was negligible on our main outcome, as shown in Table S1. The results of the multivariable linear regression indicate that, after adjusting for potential confounding factors due to the population imbalances, the only meaningful association was between preoperative gabapentin administration and improved postoperative pain control.

It seems indeed clear that, in our study, the potential for respiratory depression and sedation induced by gabapentin appeared to be the primary reason for avoiding its prescription in COPD patients. In our center, the oral dose of gabapentin is administered 1–2 h before surgery, while the patient is still in the ward and not being closely monitored by a clinician. This adds an element of caution to gabapentin prescription in patients with respiratory impairment. It is important to note, however, that we did not observe any respiratory side effects during preoperative and postoperative monitoring. While our data support the safety of a single, low-dose gabapentin administration—particularly given the absence of observed respiratory side effects—it also raises questions about the conventional hesitance in prescribing this drug to patients with respiratory conditions such as COPD and OSAS. Future studies could explore whether this caution is warranted or if it represents an overly conservative approach that potentially limits effective pain management options for these patients.

Beyond the baseline differences between the two groups, the main result of our analysis is that preoperative administration of a small dose of gabapentin is associated with better postoperative pain control at 6, 12, 18, and 24 h after surgery. Thus, the effect of a single dose of gabapentin seems to be limited to the first postoperative day, as pain scores were similar between the two groups more than 24 h after surgery. This finding partially aligns with gabapentin's pharmacokinetic properties after a single oral administration, with

a half-life ranging from five to seven hours. The absence of pain immediately after surgery and the lack of difference between the two groups three hours post surgery can be attributed to the spinal anesthesia used for the procedure, which introduces significant background noise. The persistence of gabapentin's effect for 24 h post surgery is also questionable, given its short half-life. However, our experimental data are consistent with studies showing that gabapentin's plasma concentration remains detectable for up to 36 h after a single oral administration, as demonstrated in healthy volunteers [22]. Moreover, in our context, gabapentin's half-life might have been prolonged and elimination slowed for two main reasons: the use of spinal anesthesia and the intraoperative blood losses. These factors may cause renal hypoperfusion secondary to vasodilation and hypovolemia, potentially impacting gabapentin excretion, which is almost entirely renal. These features may further explain the extent of the effect observed in this analysis among patients receiving a single dose of gabapentin, as well as the association between preoperative gabapentin administration and reduced opioid consumption during the entire hospitalization. Another important factor that may have played a role is the synergistic effect of different analgesic drugs, which has already been discussed in the literature [35,36]. This is a key pathophysiologic rationale that supports opioid-sparing anesthesia techniques. A prospectively designed trial in a similar context could further elucidate the potential role of all these elements.

The reduction in opioid administration is a significant finding, given the growing evidence of opioid-related side effects and dependence/tolerance phenomena [37]. Opioid-induced nausea and vomiting can potentially decrease the quality of postoperative pain control. Neuroadaptation phenomena following opioid administration can lead to opioid-induced hyperalgesia (OIH) and pharmacologic tolerance [37]. OIH may paradoxically worsen pain control in patients taking higher doses of opioids. Synthetic and short-acting opioids are more frequently associated with this phenomenon [38]. Tolerance increases the amount of drug needed to achieve the therapeutic effect. It has been demonstrated that perioperative overprescription, similar to prescriptions for chronic pain, plays an important role in the "opioid crisis" in North America [38]. Opioid-induced immunosuppression is another side effect to consider, potentially increasing the risk of infectious complications in the postoperative period [39]. All these observations continue to encourage the use of alternatives to opioid administration, thereby supporting opioid-sparing and opioid-free anesthesia. Using fewer opioids is associated with several benefits to the patient and may improve the quality of care perceived by patients [36].

5. Conclusions

In our study, the preoperative administration of a low dose of gabapentin in patients undergoing THA or TKA was associated with better postoperative pain control during the first 24 h after surgery and with lower postoperative opioid consumption.

The main limitations of our analysis are its observational design and the presence of possible confounders: baseline comorbidities, the arbitrary choice to perform a peripheral nerve block, and the use of NSAIDs and paracetamol during the postoperative period. However, differences in baseline comorbidities between the two populations were shown to be irrelevant to our results in the multivariable logistic regression. Analgesic drugs other than opioids were administered according to an internal protocol, and the total amount administered was similar between patients who received and did not receive a preoperative dose of gabapentin. The percentage of patients receiving a peripheral nerve block, another potential confounder, was also similar between the two groups.

Larger, randomized controlled studies that consider similar prescribing patterns should be conducted to confirm our observations. A standardized approach is desirable to avoid the heterogeneity highlighted in the numerous meta-analyses performed on this topic [27–32].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/anesthres1030017/s1, Table S1: Linear mixed model to test the effect of gabapentin preoperative administration at different postoperative timepoints; Table S2: Multivariable linear regression to test the effect of possible confounders on the association between preoperative gabapentin administration and postoperative pain.

Author Contributions: Conceptualization: A.F., A.M.P. and O.T.; Methodology: A.F., T.P. and O.T.; Software: A.F. and T.P.; Validation: R.N., R.F., W.T., G.V., A.D.F. and S.R.; Formal analysis: A.F. and T.P.; Investigation: A.F., A.M.P., R.N., R.F., W.T. and O.T.; Resources: O.T.; Data curation: A.F. and A.M.P.; Writing—original draft preparation: A.F. and O.T.; Writing—review and editing, A.F., A.M.P., T.P., G.V., A.D.F., S.R. and O.T.; Visualization: A.F. and T.P.; Supervision: G.V., A.D.F., S.R. and O.T.; Project administration: O.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of National Orthopedic Hospital Cappagh (NOHC-2022-ETH-DC-CEO- 339, date of approval: 15 September 2022) for studies involving humans.

Informed Consent Statement: Patient consent was waived due to the retrospective design of the study and due to complete data anonymization during data collection, accordingly to the information given to the Ethical Committee before study approval.

Data Availability Statement: All data are available on request in appropriate datasets.

Acknowledgments: The authors acknowledge all the nursing staff of National Orthopedic Hospital Cappagh for their precious daily activity, without which this work would not have been possible.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

THA, total hip arthroplasties; TKA, total knee arthroplasties; LAT, large amino acid transporters; LOS, length of stay; PACU, post-anesthesia care unit; ASA, American Society of Anesthesiologists; NRS, Numerical Rating Scale; LOS, hospital lenth of stay; LFCN, lateral femoro-cutaneous nerve; iPACK, interspace between the popliteal artery and capsule of the knee; SpO_2, oxygen peripheral saturation; MAP, mean arterial pressure; C_{et}, effector site concentration; NSAIDs, Non-Steroideal Anti Inflammatory Drugs; CKD, chronic kidney disease; OPG, Oregon Pain Guidance; ANOVA, Analysis Of Variance; RG, receiving gabapentin; NRG, non-receiving gabapentin; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; BMI, body mass index; POD, postoperative delirium; GA, general anesthesia; PONV, postoperative nausea and vomiting.

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