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Perioperative Gabapentin Does Not Reduce Postoperative Delirium in Older Surgical Patients: A Randomized Clinical Trial

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Abstract

Background—Postoperative pain and opioids use are associated with postoperative delirium. We designed a single center, randomized, placebo-controlled parallel-arm, double-blinded trial to determine whether perioperative administration of gabapentin reduced postoperative delirium after noncardiac surgery.

Methods—Patients were randomly assigned to receive placebo (n = 347) or gabapentin 900 mg (n=350) administered preoperatively and for the first three postoperative days. The primary outcome was postoperative delirium as measured by the Confusion Assessment Methods. Secondary outcomes were postoperative pain, opioids use, and length of hospital stay.

Results—Data for 697 patients were included with a mean age of 72 ± 6 years. The overall incidence of postoperative delirium in any of the first three days was 22.4%, (24.0% in the gabapentin and 20.8% in the placebo groups, the difference was 3.2%, {95% confidence interval

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The protocol can be obtained by written request to the primary author.

(CI) −3.22 to 9.72%}, P=0.30. The incidence of delirium did not differ between the two groups when stratified by surgery type, anesthesia type or preoperative risk status. Gabapentin was shown to be opioid sparing – with lower doses for the intervention group *vs.* control group. For example, the morphine equivalents for gabapentin treated group, median 6.7 mg (25th, 75th quartiles 1.3, 20.0 mg) *vs.* control groups, median 6.7 mg (2.7, 24.8) differed on the first postoperative day, p =0.04.

Conclusions—Although postoperative opioids usage was reduced, perioperative administration of gabapentin did not result in a reduction of postoperative delirium, or hospital length of stay.

Introduction

Delirium is a major challenge facing geriatric practice due to its prevalence, complex etiology, and potentially severe impact on patients and their families. One setting in which high rates of delirium are found is following major surgery. Postoperative delirium is associated with longer hospital stays, poor functional outcomes, and higher healthcare costs.[1] Despite the prevalence and clinical importance of postoperative delirium, an effective therapy to prevent its occurrence has not been identified.

Patients' risk for the development of delirium is determined by predisposing baseline vulnerabilities and exposure to factors that precipitate poor patient outcomes (such as pain or new medications associated with surgery). We and others have identified pain after surgery as an independent predictor of postoperative delirium,[2] and therefore, a potentially important and modifiable precipitating factor for adverse cognitive outcomes. Opioids are another potential risk factor, as patients with postoperative delirium also received more intravenous opioids postoperatively than those without delirium.[2]

Based on results from a pilot study, we found a promising intervention involving the use of an adjunctive non-opioid therapy to reduce postoperative pain and the consumption of opioids, which ultimately resulted in a reduction of the incidence of postoperative delirium.[3] Our main objective was to test the hypothesis that rates of delirium could be reduced through intensive supplementary pain management in addition to standard opioid analgesics after surgery. We conducted a double blind, placebo-controlled study using gabapentin as an additional agent in the treatment of postoperative pain in older patients undergoing major non-cardiac surgery.

Our specific aims were to: 1. Assess whether the administration of gabapentin was associated with decreased occurrence of delirium, 2. Determine the extent to which gabapentin-associated reductions in pain and/or opiate use reduced the occurrence of delirium, and 3. Determine whether the administration of gabapentin was associated with shorter hospital stays. We hypothesized that intensive pain management postoperatively using an adjuvant agent, gabapentin, would lead to a decrease in the amount of opioids received, a decrease in postoperative pain experienced, thereby resulting in a decrease in the incidence of postoperative delirium.

Methods

Study Design

This was a double blind, randomized, placebo-controlled study of 750 patients ≥ 65 years of age undergoing spine surgery or joint replacement surgery at the University of California, San Francisco Medical Center. The study received approval from the institutional review board and all patients provided written informed consent. The trial was registered with clinicaltrials.gov (updated in April 2017 to clarify primary outcome) (NCT00221338) and conducted in accordance to the original protocol. We formed a Data and Safety Monitoring Board (DSMB) to monitor participant safety, data quality and evaluate the progress of the study (appendix 2).

Participants

Potential subjects were recruited within one week before the planned surgical procedure. The inclusion criteria included patients ≥ 65 years of age undergoing surgery involving the spine, arthroplasty of hips or knees who were fluent in English, and with an anticipated length of hospital stay of at least three days after surgery. These types of patients were selected because they have substantial pre-operative and post-operative pain, and had a high incidence of postoperative delirium.[2]

Exclusion criteria included patients with known sensitivity to gabapentin, use of preoperative gabapentin, pregabalin or other anti-epileptics, spinal surgery that was two-staged involving more than one surgical procedure to be performed within the same hospitalization period, emergency surgery, preoperative renal dialysis, or “opioid tolerance” (total daily dose of an opioid ≥ 30 mg morphine equivalent for more than one month within the past year, source: Institutional Chronic Pain Management Center).

Randomization

A simple randomization method was used for this trial. Randomization into placebo or the gabapentin groups was created by a computerized random number generation method by the study statistician using a 1:1 randomization ratio. Randomization occurred after consent for study participation was obtained during the preoperative interview.

Blinding

The randomization schedule was blinded from the investigators and treating clinicians as it was kept and administered by the central research pharmacy. The assignment of gabapentin *vs*. placebo was made on the day of surgery and the study drug was delivered by the research pharmacists directly to the preoperative holding area, to be administered by clinical nurses to the study patients.

Clinical Management

A balanced anesthetic was administered for study patients who underwent spinal surgery which included a volatile anesthetic agent and intravenous agents such as propofol and fentanyl. Preoperatively, a femoral nerve block was placed for patients undergoing knee arthroplasty, and a lumber plexus block was placed for patients undergoing hip arthroplasty.

Ropivicaine was used for both blocks. In addition to the blocks, the patients undergoing arthroplasty typically received either spinal anesthesia or general anesthesia. Postoperatively, all patients who had undergone spine surgery received on-demand Patient Controlled Analgesia (PCA) with intravenous hydromorphone. for patients who underwent arthroplasty, postoperative analgesia was administered via the femoral nerve block or the lumbar plexus block for the first two postoperative days. In the case of additional analgesia for patients with incomplete analgesia from regional analgesia (<10% of cases), typically intravenous hydromorphone was administered via patient controlled analgesia; and p.o. hydrocodone/acetaminophen, oxycodone/acetaminophen, or oxycodone were administered on demand by nurse administration.

Gabapentin Dosing Regimen

We administered either gabapentin 900 mg (or placebo) p.o. 1–2 h before surgery and anesthesia. This dose continued postoperatively for the first 3 days (300 mg t.i.d). We adjusted the dose of gabapentin based on patient's pre- and post-operative renal function as previously described.[4] The rationale of choosing a clinical dose of 900 mg was based on a previous study which demonstrated that this dose was well tolerated by older patients with herpes zoster and was effective in reducing the median pain level from baseline by >50%.[5] Larger doses used in previous studies targeted primarily relatively healthy and younger surgical patients.[6–15]

Measurement of Cognitive Status

Trained research assistants who were blinded to the study drug assignment conducted cognitive tests preoperatively to determine the presence of delirium and to determine baseline cognitive function. The cognitive testing occurred in the preoperative clinic or ward, and was repeated again daily for three days after surgery. Preoperative cognitive status was measured by the Telephone Interview of Cognitive test (TICS)[16] which was adapted from the Mini Mental State Examination for use either in person or over the phone. To minimize patients' test burden, we used the 9-item word list test in lieu of the word naming in TICS during the preoperative testing.[1]

Endpoints

The primary outcome was postoperative delirium as measured by the Confusion Assessment Methods. Secondary outcomes included postoperative pain and opioids use, and the length of hospital stay.

Measurement of the primary outcome – postoperative delirium

For the occurrence of delirium, we used the Confusion Assessment Method Rating Scale (CAM)[17] which was developed as a screening instrument based on operationalization of DSM-III-R criteria for use by nonpsychiatric clinicians in high-risk settings. CAM has a sensitivity of 94–100%, a specificity of 90–95%, a high inter-observer reliability,[17] and a convergent agreement with four other cognitive status tests. Identifying delirium requires the

[1]The following cognitive tests were administered: the Word List Learning, the Digit Symbol Test, the Controlled Verbal Fluency Test. Results are not included in this manuscript.

presence of acute onset and fluctuating course, inattention, and either disorganized thinking and/or altered level of consciousness as measured by the CAM rating scale. Training of the research assistants in the use of the CAM was described in our prior publication.[17]

At approximately 24 hours after surgery, the patient was rated on the Richmond Agitation and Sedation Scale. [18] If a patient was too sedated to be interviewed (RASS score of −4 or −5), delirium status would be considered unevaluable. The severity of delirium was measured using the Memorial Delirium Assessment Scale (MDAS),[19] an instrument that contains 10 items utilizing information from the Mini Mental State Exam and structured interview to rate delirium severity.

Measurement of secondary outcomes

During each assessment of cognitive status and delirium, patients rated their pain using the 11-point verbal version of the visual analog scale (0 = no pain and 10 = the worst pain imaginable). Postoperative intravenous opioids use was measured for the first three postoperative days. We converted all opioids to morphine equivalents as follows: hydromorphone and fentanyl doses were converted to morphine equivalents using the conversion formula: 1.5 mg of hydromorphone = 10 mg of morphine equivalents, 0.1mg of fentanyl = 10 mg of morphine equivalents. [20–22] Detailed conversion for all opioids are shown in appendix 3. Postoperative length of stay was measured and compared between interventional and control groups.

Measurement of Other Covariates

Preoperative risk was measured using the American Society of Anesthesiologists (ASA) physical classification[23] and the Charlson comorbidity index.[24] Mood was measured using the standard screening tool for geriatric depression, the 15-question Geriatric Depression Scale (GDS).[25] Other covariates included functional status including Activities of Daily living (ADL) and Instrumental Activities of Daily living (IADL). Independence in ADL and IADL was determined by asking the subjects if they needed help of another person to do the activity.

Sub-group analyses

For sub-group analysis which was pre-planned, we stratified patients by preoperative risk status: low risk was defined as patients with risk scores of ≤3 and high risk with risk score of >3 based on our prior risk prediction index where one point was assigned each to female gender, history of central nervous system disorder, high surgical risk and age >75 years. A TIC score between 30–35 was assigned one point and a TIC score <30 was assigned two points.[26]

We controlled for the severity of the surgical procedures such as duration and blood loss statistically (see statistical analysis section for details). Briefly, surgical risk was estimated by taking into consideration the type and duration of surgery, and intraoperative blood loss.[27]

Measurement of In-hospital Drug-related side effects, and Complications

In addition to the primary and secondary outcomes in the study, we also measured the frequency of other potential drug-relate side effects and the occurrence of other non-fatal postoperative adverse outcomes (appendix 4) using pre-defined criteria developed by our previous studies.[28, 29]

Sample size calculation

The sample size was calculated based on the ability to detect a significant difference in rates of delirium between interventional *vs.* placebo groups with an absolute difference in delirium rate of 10% (25% vs 15%) with 90% power. The level of significance was set at two-sided alpha = 0.05 to support the hypothesis that the delirium rates in the gabapentin group was different than that in the placebo group. The rates of delirium described above were determined using a combination of our earlier published pilot data of gabapentin delirium[3] and rates of delirium among over 500 subjects enrolled in our prospective observational study.[2]

Statistical analysis

All primary and secondary outcomes were analyzed according to the intention to treat paradigm. For the primary outcomes - to compare the postoperative delirium rates between gabapentin and placebo groups, we performed a chi-square test to determine the association between gabapentin administration and delirium rate. For the secondary outcomes – subjectively reported pain scores by the visual analog scale (VAS) were stratified into low (1–3), medium (4–6), or high (7–10) for each postoperative day. The difference in pain levels was measured by chi-square between gabapentin and placebo groups. Opioid use was defined as low *vs.* high. Cut-off value for opioid dose use was based on the top 3rd quartile (75th percentile) on three postoperative days respectively. Specifically, a daily use of >22 mg of morphine equivalents in a 24 hour period was considered to be the top 75th percentile of opioid doses - high dose. Low opioid use was defined as patients who used ≤22 mg of morphine equivalents in a 24 hours period. The justification of stratifying opioids dose into high *vs.* low dose for analysis was based on our prior work on a model of prediction of postoperative delirium. [26] The difference in morphine equivalent dosing on postoperative day 1 between the gabapentin and placebo groups was determined by the Mann Whitney U Test. Hospital lengths of stay between groups were compared using the unpaired t-test.

In sub-group analyses, we conducted post-study stratification of clinical characteristics relevant to translation of results. Postoperative delirium rates were stratified by surgery type, anesthesia type, dose of postoperative opiates and pain, and preoperative risk, and reported P-values were adjusted using Bonferroni correction as needed.

In addition, logistic regression was performed to analyze the effect of gabapentin on postoperative delirium with gender and ADL as covariates. For other outcome variables of interest, including the MDAS, P-values were calculated based on Chi-square test if the variables were categorical; otherwise P-values were based on independent t-tests or Mann Whitney U test for data that were not normally distributed. To compare delirium-free days between the two treatment groups, we performed the Mantel-Haenszel test to take into

account the ordinal distribution of delirium free days. All data were reported as mean ± SD. Median values (25^{th}, 75^{th} quartiles) were included if the data were not normally distributed.

Results

Patient Recruitment

The study began in January 2006 and ended in January 2014. The patient recruitment scheme is depicted in figure 1. Overall, 697 patients were included in this intention to treat algorithm. 198 patients had total hip arthroplasty, 183 had knee arthroplasty and 316 underwent spine surgery. The demographic variables of the patients who received gabapentin vs. placebo are shown in table 1. Overall, there were more women (55.1% *vs.* 45.5%), and more patients who were dependent in one or more activities of daily living (34.4% *vs.* 25.7%) in the gabapentin compared to the placebo groups.

Completion of study drugs

The compliance of study drugs received by patients was similar between the gabapentin vs. the placebo treated patients. All patients received the preoperative study drugs. For the first postoperative day: 88.6% of patients in the gabapentin treated group completed the assigned dosing vs. 92.8% of the patients who received placebo; for the second postoperative day, 80.9% of patients in the gabapentin vs. 80.6% of the placebo groups; and for the third postoperative day, 43.1% of patients in the gabapentin vs. 39.6% of the placebo groups. The lower rate of receiving study drugs on the third postoperative day was in part due to earlier unanticipated discharge (84% of patients who did not receive the study drug or placebo were discharged earlier than anticipated).

Study outcomes measurement - primary and secondary outcomes

No patient had preoperative delirium. The overall incidence of postoperative delirium in any of the first three days for the entire cohort was 22.4%, 95% CI 19.3% −25.5% (24.0% in the gabapentin group, 95% CI 19.2% − 28.8%, and 20.8% in the placebo group, 95% CI 16.2% − 25.4%). The difference of 3.2%, {95% confidence int erval (CI) −3.2 to 9.7%}, was not statistically significant, P=0.30. When stratifying by surgery type (table 2) or anesthesia type (table 3), the incidence of postoperative delirium was also not significantly different between the gabapentin *vs.* the placebo groups.

Pain scores for the first three postoperative days are shown in table 4. Overall, patients who experienced high postoperative pain levels had higher rates of postoperative delirium compared to those with lower pain levels {19.5%, (95% CI 14.9% − 24.1%) *vs* .9.1%, (95% CI 6.3% − 11.9%), P = 0.0001}. However, the delirium rates were not significantly different between the gabapentin and the placebo groups when stratified by pain levels - delirium in low pain level group was 9.2%, 95% CI 5.5% − 14.8% (gabapentin) *vs.* 6.9%, 95% CI 3.5% − 12.7% (placebo), P= 0.16; in the medium pain level group 11.6%, 95% CI 6.2% − 20.2% (gabapentin) *vs.* 15.6%, 95% CI 9.8% − 23.5% (placebo), P = 0.52; and in the high pain level group 33.4%, 95% CI 22.0% − 44.6% (gabapentin) *vs.* 17.1%, 95% CI 9.7% − 27.8% (placebo), P = 0.05. Data for postoperative days two and three were similar (table 5).

Despite the lack of effect on postoperative delirium, gabapentin was shown to be opioid sparing, particularly in the first postoperative day. For example, morphine equivalents are lower for the gabapentin treated group, median (25^{th}, 75^{th} quartile) − 6.7 mg (1.3, 20.0 mg) when compared with the *c*ontrol group − 6.7 mg (2.7, 24.8 mg) for the first postoperative day, p =0.04 based on the Mann Whitney U Test. Note this test compares the rank sum between the two groups. Boxplots of the opioids use for the first three days are shown in figure 2. The amount of postoperative opioids use and pain level was not associated with postoperative delirium (table 5).

When we stratified patients with respect to their preoperative risk of developing postoperative delirium, high-risk patients had significantly higher rates of postoperative delirium than low risk patients. However, the rates of delirium on any of the postoperative days were not significantly different between the gabapentin and the placebo groups with preoperative risk stratification. The incidence of postoperative delirium in any of the first three postoperative days was 21% in the low risk gabapentin *vs.* 18.8% in the low risk placebo groups (P=0.56); and 47.5% in the high risk gabapentin vs. 39.4% in the high risk placebo groups (p=0.65).

We also compared the severity of delirium using the MDAS. Again, comparison of the MDAS scores between the gabapentin and placebo treated groups were not different for each of the three postoperative days (day 1 – 5.2 ± 2.8 *vs.* 5.2 ± 2.5, P=0.85; day 2 – 4.6 ± 2.7 *vs.* 4.9 ± 2.8, P=0.35; day 3 – 3.8 ± 2.4 *vs.* 4.1 ± 2.1, P=0.37).

All study patients had delirium data for one or more of the first three postoperative days. For those with missing delirium data for one or two of the three postoperative days (n=102), we determined whether missing data might bias the results. Overall, patients with missing delirium data compared to those with no missing data were younger, more likely to be male, had higher level of education, a higher incidence of alcohol use, a lower incidence of a history of central nervous system disorders, were less likely to be dependent on one or more activities of IADL, and had lower mean Charlson Comorbidity scores. Excluding the 102 patients with incomplete delirium assessments, the rates of delirium between gabapentin and placebo groups were 28.0% *vs.* 24.4%, 95% CI of the difference −3.8 to 11.0%, P=0.67. This comparison suggests those patients with missing delirium data did not have co-variates that were associated with an increased risk of postoperative delirium.

We further evaluated whether patients who were treated with gabapentin had a difference in delirium-free days for the first three postoperative days when compared with placebo treated patients. This analysis included all intention-to-treat patients with a hospital length of stay of 3 days or longer and patients with missing delirium data were excluded. Again, the comparison did not show any difference between the two groups (table 6).

As to the secondary outcome - the length of hospital stay in patients with postoperative delirium was significantly longer than those without delirium (5.5 ± 3.1, 95% CI 5.2 – 5.8 days *vs.* 3.9 ± 2.8 days, 95% CI 3.6 – 4.2 days, P<0.0001). However, there was no difference in length of hospital stay between patients treated with gabapentin *vs.* placebo (4.4 ± 3.4 days, 95% CI 4.0 – 4.7 days *vs.* 4.1 ± 2.3 days, 95% CI 3.9 – 4.3 days, P=0.26).

Safety evaluation of gabapentin administration

Regarding the safety of perioperative gabapentin administration, we measured postoperative clinically significant over-sedation as determined by the RASS scores and also postoperative adverse events. Overall, the incidence of serious over-sedation rates (RASS scores of −4 or −5) were not different on any of the postoperative days between the gabapentin or placebo groups (day 1 2/333 = 0.6% vs. 1/329 = 0.3%, P=0.61; day 2 4/321 = 1.3% vs. 1/328 = 0.3%, P=0.37, and day 3 0/289 = 0% vs. 1/284 = 0.4%, P=0.60). Detailed comparison of the RASS scores is shown in table 7. We also compared other potential drug-related side effect such as dizziness and no significant difference was found between study groups – 10/345 patients (2.9%) in the gabapentin *vs.* 5/340 patients (1.5%) in the placebo groups (P=0.30). No patient reported nystagmus or ataxia in either study groups. The incidence of adverse postoperative events relating to the cardiovascular, pulmonary, renal, neurological systems, and infection and thrombotic events also was not significantly different between gabapentin *vs.* placebo treated groups (8.9% *vs.* 12.7%, P=0.13).

Discussion

This large prospectively conducted randomized clinical trial revealed no difference in rates of postoperative delirium when gabapentin was administered perioperatively to older surgical patients when compared with placebo, despite its opioid-sparing effects.

Comparison with previous studies

Aside from our prior pilot study,[30] no previous study has investigated the use of perioperative gabapentin as a means to reduce postoperative delirium. However, there have been a number of other pharmacological interventional trials aimed at delirium reduction in surgical patients but with mixed results. Most studies found no effects of pharmacological treatments with anti-psychotics or anti-cholinesterase agents on delirium reduction.[31–33] While several small studies have suggested anti-psychotics may reduce the risk of delirium, these finding were not supported by meta-analyses. [34, 35] Moreover, the prophylactic administration of both conventional and atypical anti-psychotics to the older patients is potentially hazardous, with cardiac and metabolic side effects reported because of age-related changes in pharmacokinetics and pharmacodynamics as well as potential adverse drug interactions with other medications.[36] Hence, the evidence to date does not support the use of antipsychotics for prevention of postoperative delirium.

Other types of intervention reported involved the evaluation of sedatives or anesthetic agents such as dexmedetomidine or ketamine. [37, 38] However, these clinical trials produced mixed results and definitive therapies based on trials with adequate sample size are yet to be developed. A recent large trial in postoperative patients recovering in the intensive care unit reported that intravenous infusion of dexmedetomidine immediately after surgery reduced the occurrence of postoperative delirium when compared with placebo. [39] Whether these results can be generalized to non-ICU patients remain to be determined. In contrast to pharmacologic prophylactic treatment, non-pharmacologic intervention such as fast track surgery,[40] specialized postoperative geriatric wards,[41] and proactive geriatric consultation[42] reported more success in delirium reduction. Thus, a recent systematic assessment

conducted by the American Geriatrics Society concluded that only non-pharmacologic interventions were proven to be efficacious and should be widely practiced. Recently, it has been proposed that deep anesthetic depth contributes to an increased rate of postoperative delirium. [43–46] However, the mechanism of this deep anesthesia effect has not been completely elucidated despite a recent report that burst suppression on electroencephalogram indicative of deep anesthesia may have been the etiologic factor.[46]

Our results did not support the second hypothesis that gabapentin-associated reductions in pain and/or opiate use reduced the occurrence of delirium. Although we did find that gabapentin was opioid sparing, we did not demonstrate that the opioid-sparing effect resulted in a reduction of postoperative delirium. It is likely that the opioid-reducing effect of gabapentin was attenuated by the concomitant use of postoperative analgesia such as femoral nerve block or lumbar plexus block in some of our patients who underwent arthroplasty. This explanation is in part supported by prior studies which demonstrated that reducing opioid exposure may be achieved with regional analgesia such as femoral nerve block or fascia iliaca block, [47, 48] both of these techniques have been shown to be associated with lower risk of postoperative delirium, but definitive large-scale trials are lacking.

A recent meta-analysis examined the effect of preoperative gabapentin in reducing postoperative opioid consumption. [49] In the 17 randomized trials that were examined, the dosages of gabapentin ranged from 300 mg to 1,200 mg. Our study chose the 900 mg preoperative dose, which is within the range identified in this review. Of note that meta-regression analyses identified a statistical association between reduced postoperative opioid consumption and gabapentin dosage. [49]

Potential study limitations

First, despite a computerized randomization of recruited patients, we observed some unbalance across treatment groups with respect to preoperative patient characteristics. However, inclusion of the co-variates that were different between groups did not affect results of the outcome measurements. Second, we studied patients with three types of surgery, and the methods of intraoperative anesthetics and postoperative management were different between groups. However, inclusion of the type of surgery and anesthetics as co-variates did not affect the rates of postoperative delirium between the gabapentin treated and placebo groups. Third, because of changing perioperative practice patterns during the duration of the study, the inclusion of multi-modal oral analgesics such as acetaminophen and non-steroidal anti-inflammatory agents administered to the placebo patients who underwent arthroplasty surgery perioperatively might have resulted in lower rates of postoperative delirium in that group when compared to historical controls. Lastly, we did not specifically measure other opioids related side effects such as pruritus, nausea, vomiting, *etc.* and whether gabapentin through its opioid-sparing action produced salutary effects will need to be determined by further investigations.

Summary

Results from this large randomized double-blind, placebo controlled trial showed that perioperative administration of gabapentin did not result in a lower rate of postoperative

delirium in older patients undergoing major spine and arthroplasty surgery, despite its opioid sparing effects. Our results suggest that the prophylactic use of gabapentin as a mean to reduce postoperative delirium is not indicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary Statement

Our study showed that perioperative gabapentin administration as an add-on agent was opioid sparing but did not reduce the incidence of postoperative delirium in older patients undergoing noncardiac surgery.

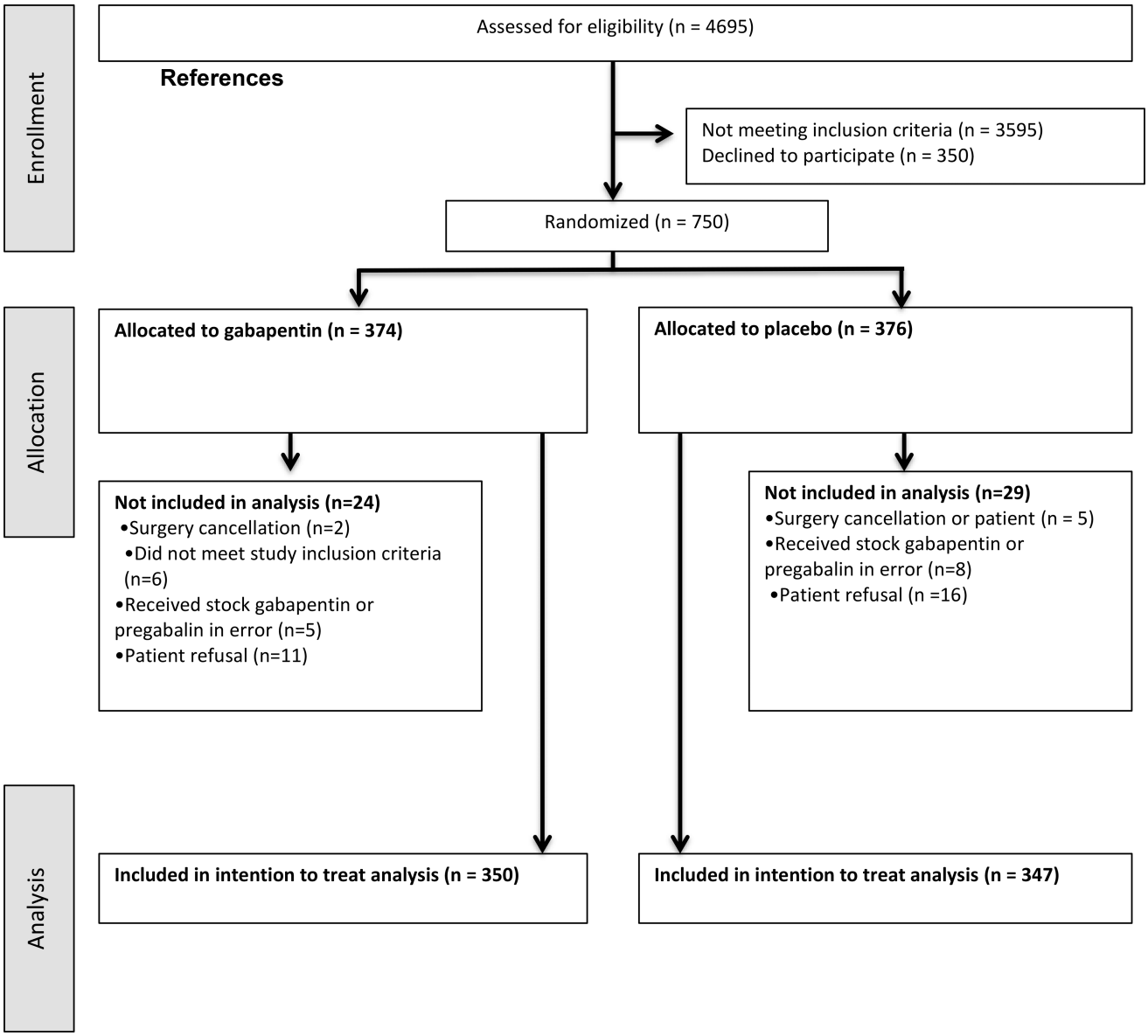
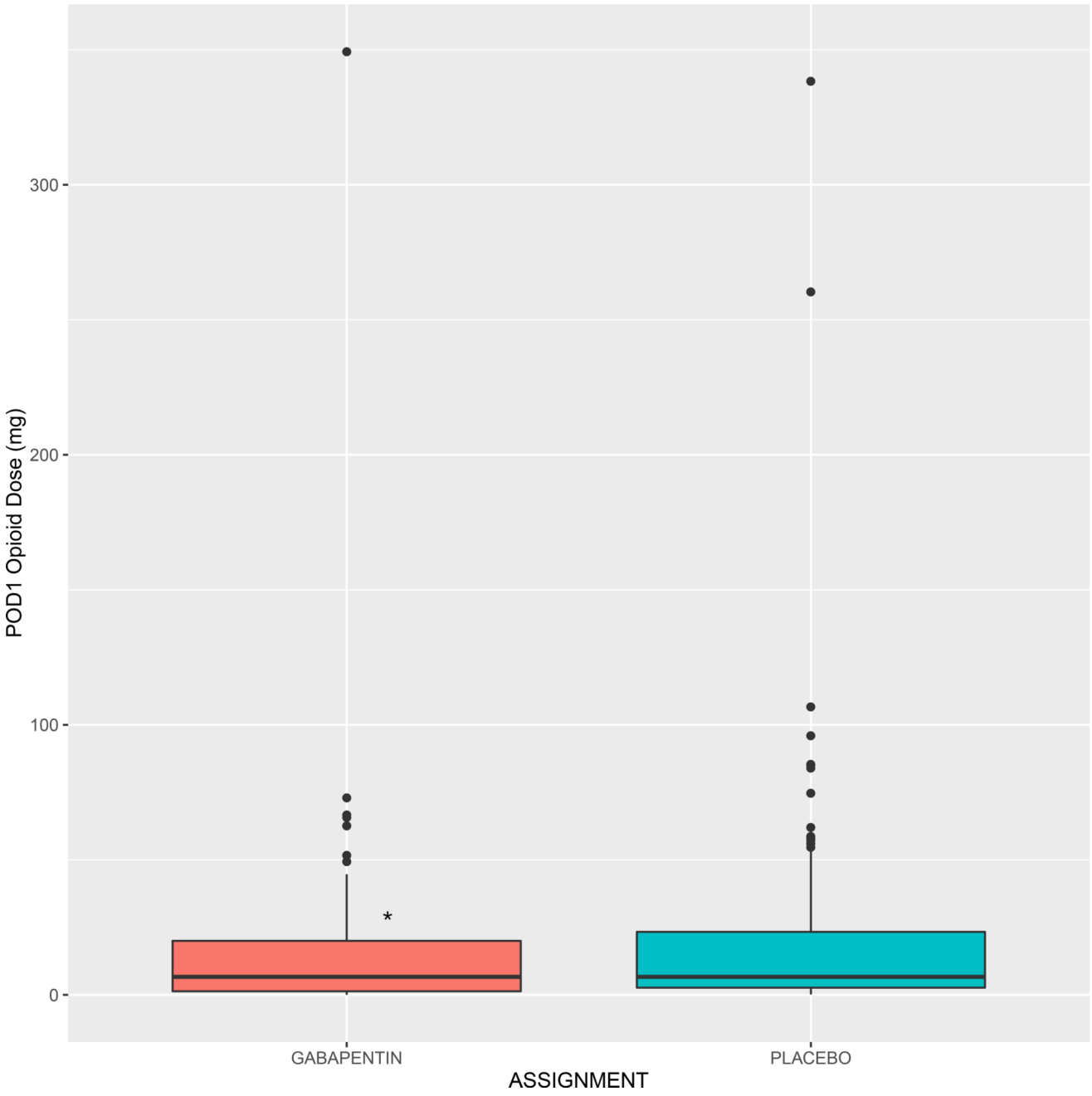
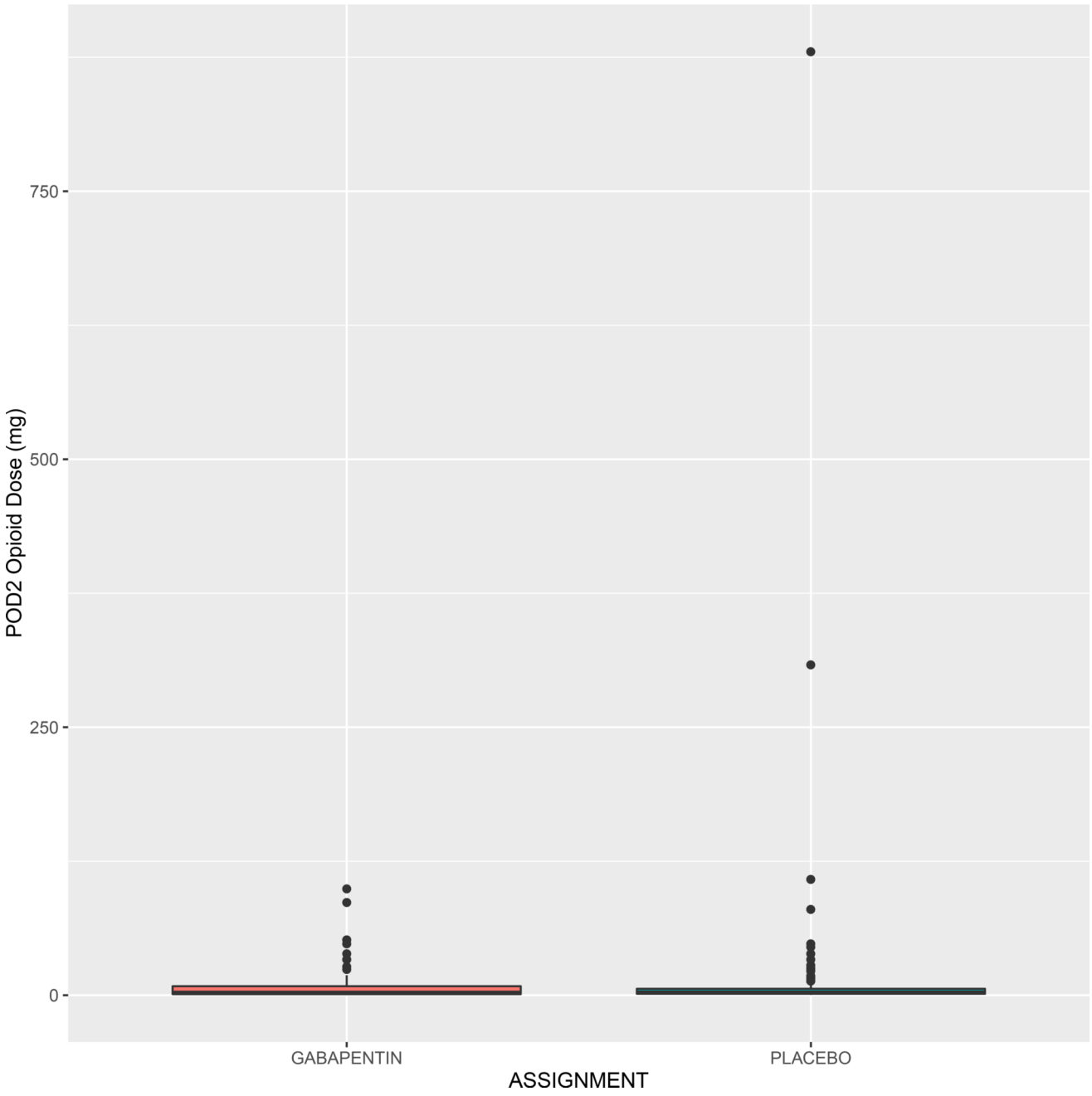


Figure 1.
The consort diagram depicting patient recruitment scheme is shown in this figure





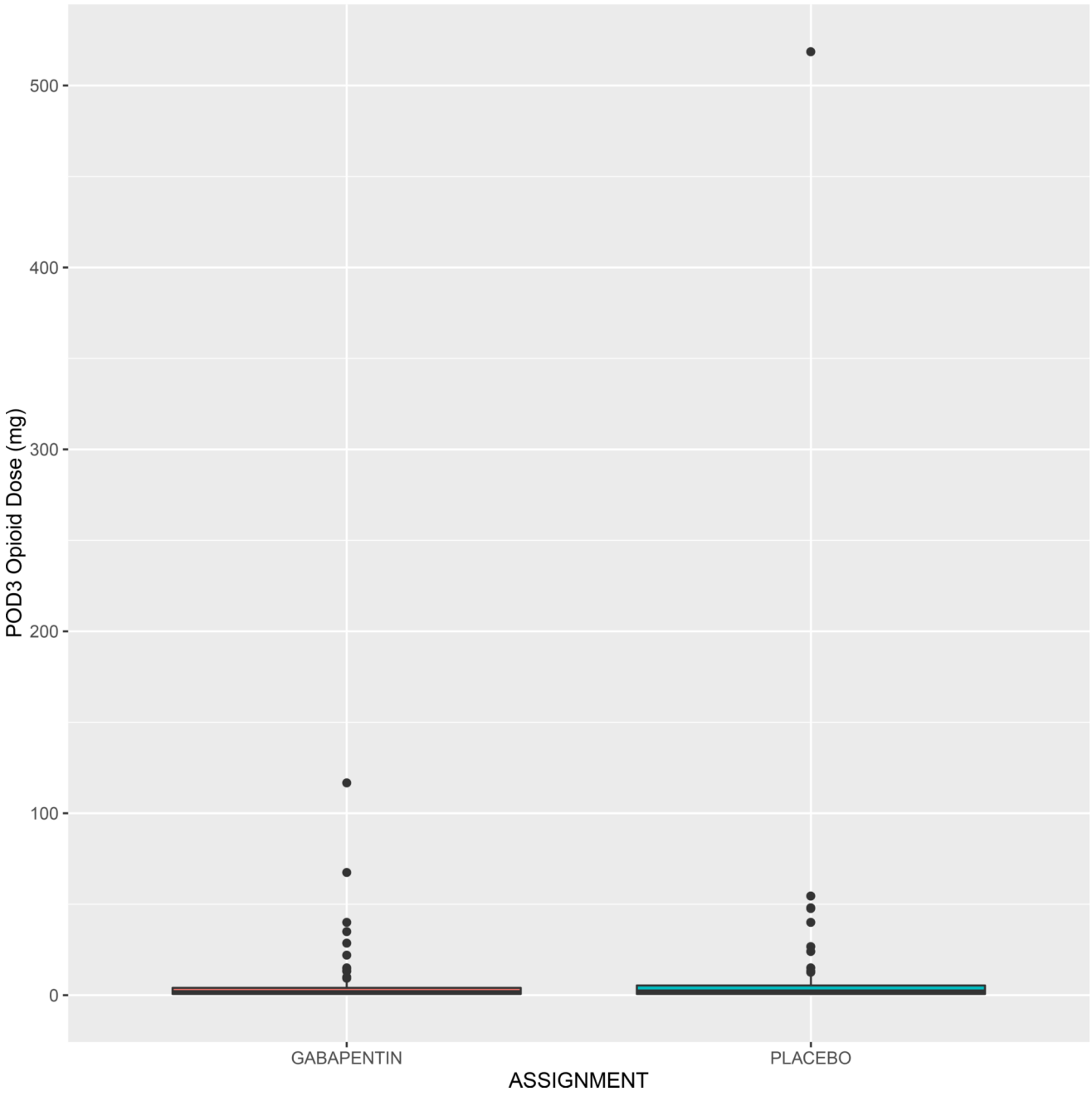


Figure 2.

a Boxplots of opioids use (in morphine equivalents) for the first postoperative day (POD) is shown in figure 2a. The gabapentin and placebo groups are shown on the X-axis. On the Y-axis is shown the morphine equivalents (mg). A typical box plot showed the median (thicker black line in the middle of the box), and first and third quartiles represented by the bottom and the top of the box respectively. The median (25^{th}, 75^{th} quartile) of morphine equivalents for the gabapentin treated group − 6.7 mg (1.3, 20.0 mg) *vs.* control groups − 6.7 mg (2.7, 24.8) differed on the first postoperative day, p =0.04. The asterisk indicates significant

difference between the gabapentin *vs.* placebo groups based on Mann Whitney U test. See text for details.

b Boxplots of opioids use (in morphine equivalents) for the second postoperative day (POD). The median morphine equivalent dose in the gabapentin group was 1.0 (2.3–8.4 mg), vs. 1.0 (2.7–6.0 mg) in the placebo group, P= 0.48.

c Boxplots of opioids use (in morphine equivalents) for the third postoperative day (POD). The median morphine equivalent dose in the gabapentin group was 0.7 (1.7–4.0 mg), vs. 0.7 (2.0–5.3 mg) in the placebo group, P= 0.72.

Table 1

Comparisons between Drug Assignment Groups: Surgical/Anesthetic factors

Variable	GABAPENTIN (N=350)	PLACEBO (N=347)	P-value
Age (years, mean and sd)	73 ± 6	73 ± 6	.10
Gender, Female	193 (55.1%)	158 (45.5%)	.01
Race, White	323 (92.3%)	315 (90.8%)	.33
Ethnicity, Hispanic	10 (2.9%)	11 (3.2%)	.81
Education, College or higher	218 (62.3%)	217 (62.5%)	.95
Alcohol Use, ≥2 drinks/day	25 (7.1%)	31 (8.9%)	.38
At least one of 5 ADLs	43 (12.3%)	25 (7.2%)	.03
At least one of 7 IADLs	206 (58.9%)	194 (55.9%)	.45
Preoperative GDS, ≥6	50 (14.3%)	42 (12.1%)	.41
Preoperative TICS score (mean ± sd)	34.5 ± 3.5	34.5 ± 3.1	.89
History of CNS disorder, Yes	208 (59.4%)	213 (61.4%)	.65
Charleston Comorbidity Index (mean ± sd)	0.5 ± .9	0.6 ± .1.0	.43
ASA III/IV	119 (34%)	128 (36.9%)	.43
Surgical Risk II	336 (96.0%)	334 (96.3%)	.86
Surgical Risk III	14 (4.0%)	13 (3.7%)	

ASA = American Society of Anesthesiologist physical classification
ADL = activities of daily living
IADL = instrumental activities of daily living
GDS = geriatric depression score
TICS = telephone interview of cognitive status
CNS = central nervous system
sd=standard deviation

Table 2

Association between drug assignment and delirium by surgery type with all ITT patients

	Hip **n/N (%) (N=198)**		**P-value**	**Knee** **n/N (%) (N=183)**		**P-value**	**Spine** **n/N (%) (N=316)**		**P-value**
Delirium on any of the first three postoperative days	Gabapentin	Placebo		Gabapentin	Placebo		Gabapentin	Placebo	
	19/101 (18.8%)	9/97 (9.3%)	0.09 (0.27)*	27/94 (28.7%)	17/89 (19.1%)	0.18 (0.54)*	38/155 (24.5%)	46/161 (28.6%)	0.49 (1.00)*
Mean difference (95% CI)	9.5 (−1.0 to 20.1%)			9.6 (−3.7 to 22.9%)			4.1 (−14.4 to 6.3%)		

* p-values adjusted by Bonferroni correction.

ITT = intention to treat

Table 3

Incident Postoperative Delirium by Drug Assignment and Anesthetic Type

Variable	GABAPENTIN (N=350)	PLACEBO (N=347)	Chi-square test: P-value
Delirium on any of the first three postoperative days			
Group 1	42/145 (30.0 %)	49/152 (32.2%)	0.63 (0.63) *
Mean difference (95% CI)	−2.2 (−14.4 to 7.9%)		
Group 2	6/23 (26.1%)	0/23 (0.0%)	0.03 (0.09) *
Mean difference (95% CI)	26.1 (4.0 to 48.4%)		
Group 3	36/132 (27.3%)	23/120 (19.2%)	0.17 (0.34) *
Mean difference (95% CI)	8.1 (−3.0 to 19.3%)		

* p-values adjusted by Bonferroni correction.

Group 1 = General anesthesia only

Group 2 = General plus regional anesthesia

Group 3 = Regional anesthesia only

Table 4

Postoperative pain scores stratified by treatment groups

	Gabapentin	Placebo
Postoperative day one	4 ± 3 (3) n=343	4 ± 3 (4) n=343
Postoperative day two	3 ± 3 (2) n=335	4 ± 3 (3) n=343
Postoperative day three	3 ± 3 (3) n=299	3 ± 3 (3) n=291

The postoperative pain scores (visual analog scores) are shown as mean ± SD and median (in brackets) for the first three postoperative days for the two treatment groups. No significant difference was found between the mean pain scores in the gabapentin *vs.* the placebo groups.

Table 5

Delirium Rate by Pain and Morphine Equivalent Dosing on the First Postoperative Day Stratified by Treatment

Treatment	GABAPENTIN	PLACEBO
Pain & Opioid		
Low & Low	15/158 (9.5%)	10/127 (7.9%)
Medium & Low	10/84 (11.9%)	17/108 (15.7%)
High & Low	17/60 (28.3%)	9/63 (14.3%)
Low & High	1/11 (9.1%)	0/14 (0%)
Medium & High	0/9 (0%)	2/14 (14.3%)
High & High	6/10 (60.0%)	3/11 (27.3%)

Morphine equivalence dosing was defined as low *vs.* high. The cut-off value for low dose use was based on the 75th percentile on three postoperative days respectively. Specifically, a daily use of >22 mg of Morphine in a 24 hour period was considered to be the top 75% of opioid doses - high dose. Low opioid uses were defined as patients who used ≤22 mg of Morphine in a 24 hours period. Subjectively reported pain scores by the visual analog scale (VAS) were stratified into low (0–3), medium (4–6), or high (7–10). The overall difference in distributions between the two groups was not significant by Wald Test Statistic = 2.89, P=0.09)

Table 6

Delirium free days for postoperative days 1–3 between GABAPENTIN and PLACEBO groups

Delirium free days	GABAPENTIN (N=295)	PLACEBO (N=293)	Mantel-Haenszel Test: P-value
0	6 (2.0%)	7 (2.4%)	0.63
1	20 (6.8%)	17 (5.8%)	
2	53 (18.0%)	47 (16.0)	
3	216 (73.2%)	222 (75.8%)	

Includes all intention-to-treat patients with the length of hospital stay ≥3 days (patients with missing delirium data were excluded)

Table 7

Bivariate association between drug assignments and postoperative sedation scores

	n/N (%) (N=697)		
Variable	**GABAPENTIN (N=350)**	**PLACEBO (N=346)**	**P-value**
Sedation on POD 1, Normal(>=0)	238/333 (71.5%)	229/329 (69.6%)	.61
Median(−1 to −3)	93/333 (27.9%)	99/329 (30.1%)	
Serious(−4 and −5)	2/333 (0.6%)	1/329 (0.3%)	
Sedation on POD 2,Normal(>=0)	247/321 (76.9%)	251/328 (76.5%)	.37
Median(−1 to −3)	70/321 (21.8%)	76/328 (23.2%)	
Serious(−4 and −5)	4/321 (1.2%)	1/328 (0.3%)	
Sedation on POD 3, Normal(>=0)	233/289 (80.6%)	229/284 (80.6%)	.60
Median(−1 to −3)	56/289 (19.4%)	54/284 (19.0%)	
Serious(−4 and −5)	0/289 (0%)	1/284 (0.4%)	

POD = postoperative day

In this table, the sedation scores were reported for three postoperative days. The P-value reflects comparison of the range of sedation scores for each specific postoperative day between study groups.