# Comparison of three different prophylactic treatments for postoperative nausea and vomiting after total joint arthroplasty under general anesthesia: a randomized clinical trial

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# Abstract

Background: Postoperative nausea and vomiting (PONV) after total joint arthroplasty is common and associated with delayed recovery. This study was performed to evaluate the efficacy of three different prophylactic regimens for PONV after total joint arthroplasty under general anesthesia.

Methods: Patients undergoing primary total hip or knee arthroplasty were randomized to Group A (8 mg ondansetron), Group B (10 mg dexamethasone plus mosapride), or Group C (three doses of 10 mg dexamethasone plus mosapride). The primary outcome was the incidence of PONV. The secondary outcomes were complete response, rescue antiemetic treatment, opioid consumption, time until first defecation, postoperative appetite score, satisfaction score, length of hospital stay, blood glucose level, and complications.

Results: Patients in Group C experienced a lower incidence of severe PONV (1.72%, $p<0.001$) and a higher incidence of complete response (70.69%, $p=0.001$) than did patients in Groups A and B. Moreover, less rescue antiemetic treatment and postoperative opioid consumption was needed in Group C ($p<0.05$). Additionally, a shorter time until first defecation, shorter length of stay, and better postoperative appetite scores and satisfaction scores were detected in patients in Group C. A slight increase in the fasting blood glucose level was observed in Group C, and the complications were comparable among the groups.

Conclusion: Prophylactic use of mosapride and three doses of dexamethasone can provide better antiemetic effectiveness, postoperative appetite, bowel function recovery, and pain relief than a single dose or ondansetron only.


# Background

Postoperative nausea and vomiting (PONV) is one of the most common and distressing complications after surgery. This is especially true in patients undergoing general anesthesia, among whom the incidence of PONV may reach 25–30% and may even rise to 80% among patients without prophylactic intervention(1, 2). Optimal management of PONV is important for rapid recovery after joint arthroplasty because effective treatments that limit post-operative nausea allow patients to mobilize earlier, decrease length of stay, and improve overall patient satisfaction(3).

Numerous precautionary measures have been taken in an attempt to prevent PONV, such as administration of $5HT_3$ receptor antagonists (e.g., ondansetron), neurokinin 1 receptor antagonists (e.g., aprepitant), corticosteroids (e.g., dexamethasone), butyrophenones (e.g., droperidol), and antihistamines (e.g., dimenhydrinate)(4). Although the efficacy of these prophylactic drugs has been confirmed by high-level evidence, PONV remains a persistent problem(5, 6). One reason for this phenomenon is the huge gap between implementation and the “PONV-free” goal. Our preliminary results indicated that the incidence of PONV was high at 48.8% in patients who underwent total joint arthroplasty under general anesthesia in our institute. Another reason for the persistence of PONV is the adverse effects associated with anti-PONV treatments, and no ideal regimen has been established. For example, use of the $5\text{-}HT_3$

receptor antagonist ondansetron can aggravate the postoperative constipation which occurs in up to57% of patients who undergo total joint arthroplasty(7). Dexamethasone, another common antiemetic agent, can reduce the incidence of PONV following total hip or knee arthroplasty(8–10), but may increase the risk of wound complications or gastrointestinal ulcers. Additionally, the most appropriate dosage and timing of dexamethasone have not been determined.

Our preliminary results also showed that the use of opioids or intravenous nonsteroidal anti-inflammatory drugs was a risk factor for PONV following primary total hip or knee arthroplasty (odds ratio = 2.052, p = 0.008; published in Chinese) because these drugs inhibit gastrointestinal peristalsis. In contrast, selective 5-$HT_4$ agonists can stimulate the gastrointestinal tract and promote motility(11), and mosapride, one type of 5-$HT_4$ agonist, is reportedly effective in reducing the incidence of vomiting caused by chemotherapy(12). To the best of our knowledge, however, very few studies have evaluated and compared the antiemetic efficacy of mosapride with that of other types of PONV prophylaxis.

Thus, in the present study, we compared the anti-emetic efficacy of concurrent use of different doses of dexamethasone and mosapride with ondansetron. We presumed that combined application of three doses of dexamethasone and mosapride would provide a greater clinical benefit.

# Patients And Methods

### *Study design*

This prospective randomized clinical trial involved patients undergoing primary total hip or knee arthroplasty from November 2017 to December 2018. Institutional review board approval (2012-268) was obtained before patient enrollment. Written informed consent and research authorization were obtained from all patients before surgery. The study was conducted in compliance with the tenets of the Declaration of Helsinki, and the study protocol was registered at the Chinese Clinical Trial Registry (ChiCTR1800015896, April 27, 2018).

### *Inclusion and exclusion criteria*

Eligible patients included those at least 18 years old who were at risk of PONV (at least 1 score of Apfel), and scheduled for primary total hip or knee arthroplasty for end-stage joint diseases such as osteoarthritis, development dysplasia of hip, and osteonecrosis of the femoral head. Exclusion criteria included a history of intolerance of any drugs used in the current study, administration of another anti-emetic drug or systemic steroid within 24 h before surgery, allergy to experimental drugs or history of adverse reactions, diabetes with poor blood glucose control, history of steroid or immunosuppressive drug use within the previous 6 months, history of cardiac disease such as heart failure, heart block, ventricular arrhythmia or severe impairment of bowel motility, renal function or hepatic function.

### *Randomization and treatment*

All patients in this triple-blinded study were randomly allocated to three groups of prophylactic treatment for PONV using a computer-generated randomization list. The group assignments were kept in opaque sealed envelopes that were only opened immediately before surgery.

- Group A received 8 mg ondansetron (4 ml) at the end of surgery; three doses of 2 ml normal saline at anesthetic induction and 6 and 24 hours later; and oral placebo 3 hours before surgery and three times per day after the operation.
- Group B received one dose of 10 mg dexamethasone (2 ml) at anesthetic induction, two doses of normal saline 6 and 24 hours later, 5 mg oral mosapride 3 hours before surgery and three times per day after the operation, and a dose of 4 ml normal saline at the end of surgery.
- Group C received three doses of 10 mg dexamethasone (2 ml) at anesthetic induction and 6 and 24 hours later, 5 mg oral mosapride 3 hours before surgery and three times per day after the operation, and a dose of 4 ml normal saline at the end of surgery.

The intraoperative dexamethasone and ondansetron were administered by an anesthesiologist, and the postoperative oral drugs were administered by nurses who were not involved in the study. The patients, surgeons, data collectors, and analysts were all blinded to the group assignments.

### *Anesthesia and perioperative pain management*

All surgeries were performed under general anesthesia by the same team (F.X.P. and Z.K.Z.) using the standard medial parapatellar arthrotomy for total knee arthroplasty and posterolateral approach for total hip arthroplasty. A cemented posteriorly stabilized prosthesis was implanted in all patients undergoing total knee arthroplasty, and cementless acetabular and femoral components were used in all patients undergoing total hip arthroplasty.

All patients received the same anesthetic regimen and multimodal pain management protocol. Cefuroxime (1.5 g) was given intravenously as a prophylactic antibiotic prior to the first incision. Sufentanil (0.2 μg/kg), propofol (2 mg/kg), atracurium (1 mg/kg), and midazolam (2 mg) were used for anesthetic induction. Sevoflurane (1%–3%) and single bolus of sufentanil (0.1 μg/kg), and atracurium (0.5 mg/kg) were then used to maintain anesthesia during surgery. After prosthesis insertion, propofol (4 mg/kg. h) and remifentanil (0.1 μg/kg. min) were used to maintain anesthesia. The anesthetic drugs were discontinued before wound closure. All patients received preoperative oral hydration for up to 2 hours prior to surgery and adequate intravenous fluids intraoperatively.

After prosthesis insertion, a periarticular infiltration of 200 mg ropivacaine (100 mg/10 ml) in 60 ml normal saline was injected around the capsule before closure. One dose of 40 mg parecoxib was injected intravenously to manage pain. Postoperative pain control consisted of 50 mg of oral diclofenac sodium (Voltaren sustained-release tablets; Novartis Pharmaceuticals, Basel, Switzerland) every 12 hours. Breakthrough pain was recorded using a Numeric Rating Scale (NRS) ranging from 0 points (no pain) to 10 points (the most severe pain). Once the patients provided feedback that the pain was at a NRS score of >4 points, 10 mg oral oxycodone was administered. If the VAS score was >6 points, 50 mg of pethidine

was given by intramuscular injection as required up to every 6 hours. No nerve block or intravenous patient-controlled analgesia was utilized perioperatively.

### *Outcome measurements*

The primary outcome was the incidence of PONV, and the secondary outcomes were complete response, times until first defecation and ambulation, postoperative appetite score, satisfaction score, length of hospital stay, blood glucose level, and complications. A blinded clinical investigator (Y.C.C.) reviewed the patients' diagnoses and medical histories and prospectively collected the demographic data and surgical information. The investigator also recorded all episodes of nausea and vomiting, the severity of nausea, the antiemetic rescue requirement, and complete response during four postoperative periods (0–6, 6–12, 12–24, and 24–48 hours) to evaluate the antiemetic efficacy. Nausea was defined as a subjective unpleasant sensation associated with awareness of the urge to vomit, and vomiting was defined as the forceful expulsion of gastric contents from the mouth [12]. The incidence of PONV was determined in each of the four periods and during the entire study by calculating the proportion of patients who experienced PONV. Following institutional guidelines, 10 mg of intramuscular metoclopramide was used as a first-line antiemetic rescue treatment when patients experienced two or more episodes of PONV within 2 hours. This was followed by administration of 4 mg ondansetron intravenously when two consecutive boluses of metoclopramide alone administered at a 30-minute interval were ineffective

We used a standardized scoring algorithm to classify the severity of PONV during the 48-hour observation period in four degrees. Complete response was defined as no PONV or no requirement for a rescue antiemetic. Mild PONV was defined as the occurrence of mild nausea or one episode of vomiting if caused by an exogenous stimulus (drinking or movement). Moderate PONV was defined as up to two episodes of vomiting or the experience of nausea that required only one dose of a rescue antiemetic. Finally, severe PONV was defined as more than two emetic episodes or the need for more than one dose of a rescue antiemetic(13).

The blinded investigator (Y.C.C.) also recorded the time of first defecation, time of first ambulation, length of hospital stays, appetite score on postoperative days 0 to 2, and patients' satisfaction score. *The patients' appetite was scored by comparison with the preoperative level (the morning on the day 1 before surgery); 1 point represented a worse appetite, 2 points represented no change in appetite from the preoperative state, and 3 points represented a better appetite.* Patients' satisfaction before discharge was estimated using a NRS that ranged from 0 points (extremely dissatisfied) to 10 points (very satisfied).

The fasting blood glucose level was measured in all patients on postoperative days 1 and 2, while the 2-hour postprandial blood glucose level was measured in patients with diabetes mellitus on postoperative day 1. All patients were followed up for 3 months postoperatively, and any complications such as prolonged QT syndrome, wound discharge, surgical site infection, or readmission were recorded.

### *Statistical analysis*

We performed an *a priori* power analysis based on our preliminary results showing that the incidence of PONV was 49% in patients receiving ondansetron prophylaxis alone after total joint arthroplasty. We calculated that 303 patients (101 in each arm) were required to detect a 45% reduction in the incidence of PONV at an alpha level of 0.05 and power of 0.9 using a two-sided test. To allow for exclusions and dropouts, we enrolled 348 patients in the current trial.

The chi-square test or Fisher's exact test was used to determine the statistical significance of differences in the categorical variables, such as the incidence of PONV and proportion of patients with complete response; if significant, multiple comparisons between groups were performed by Bonferroni's corrected *post hoc* test. Continuous variables were analyzed with one-way analysis of variance (body mass index, length of hospital stay, and times until first defecation or ambulation) or the Wilcoxon signed-rank test (patients' appetite and satisfaction scores); if significant, multiple comparisons between groups were performed by the *post hoc* Tukey test. A p value of <0.05 was considered statistically significant. Statistical analysis was conducted using SPSS 21.0 (IBM Corp., Armonk, NY, USA).

# Results

In total, 348 patients were initially allocated to Groups A, B, and C (116 patients in each group). We excluded eight patients each from Groups A and B according to the defined exclusion criteria. Thus, 332 patients (108 in Group A, 108 in Group B, and 116 in Group C) were included in the final analysis (**Figure 1**). We found no differences in demographic characteristics or clinical data among the groups (**Table 1**).

During the whole evaluation period, the incidence of postoperative nausea was lowest in Group C (15.52%), followed by Group B (21.30%) and Group A (31.48%); the difference between Groups A and C was statistically significant (p=0.005) (**Table 2**). The patients in Group C had the lowest incidence of postoperative vomiting (13.79%) when compared with Groups B (15.74%) and A (20.37%), although the difference was not significant. Similarly, more patients who received three doses of dexamethasone and mosapride in Group C achieved a complete response (70.69%) compared with Groups A (48.15%, p=0.001) and B (62.96%, p=0.219). In addition, fewer patients in Group C had severe PONV (1.72%) compared with Group B (12.96%, p=0.001) and Group A (18.52%, p<0.001).

According to the timing and duration of PONV, concurrent use of mosapride and three doses of dexamethasone mainly reduced the incidence of PONV during the first 12 hours, especially from 0 to 6 hours (**Tables 3, 4**). 94.4% of all PONV events occurred from 0 to 6 hours postoperatively in Group C, which was higher than that in Group B (82.61%, p=0.363) and Group A (47.06%, p=0.001). Of all patients with episodes of PONV in Group C, 88.89% of patients had episodes that lasted <6 hours, which was a higher proportion than in Group B (39.13%, p=0.001) and Group A (35.29%, p<0.001). The mean time of PONV in Group C was 2.89±1.71 hours, which was shorter than that in Groups A (16.18±14.95 h, p=0.002) and B (18.17±18.20 h, p=0.001).

With the use of multiple doses of dexamethasone, fewer patients needed antiemetic rescue treatment in Group C; however, the total consumption of rescue treatment was not significantly different. Moreover, the

consumption of oxycodone and pethidine in Group C was less than that in Groups B and A (**Table 5**).

The time until first defecation was 37.2±8.97 h in Group C, 46.67±11.79 h in Group B, and 52.43± 16.48 h in Group A, and all intergroup differences were statistically significant ($p<0.05$ for all) (**Table 6**). Moreover, the patients in Group C had a better appetite on postoperative day 1, were more satisfied with their healthcare, and had a shorter length of hospitalization than the patients in Groups B and A ($p<0.05$ for all).

We measured the blood glucose level to assess the safety profile of dexamethasone. Among patients with diabetes mellitus, the fasting blood glucose level was higher in Group C with three doses of dexamethasone than in Group A on postoperative day 1 (**Table 7**). Among patients without diabetes mellitus, the fasting blood glucose level was higher in Group C than Groups A and B on postoperative days 1 and 2, although the blood glucose level was acceptable in all groups. During the study and follow-up period, the incidence of complications was comparable among the three groups.

# Discussion

As an important part of an enhanced recovery after surgery program, PONV management remains a challenge during the postoperative period, especially in the setting of general anesthesia. Therefore, we should pay more attention to PONV prevention and treatment because PONV can cause anxiety and loss of appetite and can increase the risk of complications and length of hospital stay. Although some clinical guidelines and suggestions have been recommended, the incidence of PONV remains a “little big” problem because of the lack of an ideal PONV prophylaxis regimen.

In the present study, we compared three different PONV prophylactic protocols and found that with the use of oral mosapride and three doses of dexamethasone, patients experienced a lower incidence and severity of PONV from 0 to 6 hours postoperatively, a better appetite, and a higher satisfaction score. More importantly, the combined use of dexamethasone and mosapride reduced the consumption of opioids and promoted postoperative bowel function recovery, thus reducing the incidence of postoperative constipation.

Effective treatments that limit PONV allow patients to mobilize earlier, decrease the length of stay, and improve patients’ overall satisfaction. Many factors are attributable to the incidence of PONV, including female sex, a history of PONV or motion sickness, and opioid use(14). 5-$HT_3$ receptor antagonists and glucocorticoids are the most common treatment options for PONV prevention. Ondansetron, one type of 5-$HT_3$ receptor antagonist, has been recommended as the first-line agent for PONV prevention by some clinical guidelines(4). Additionally, a study by Apfel et al.(15) showed comparable efficacy in reducing the incidence of PONV between 4 mg ondansetron and 4 mg dexamethasone. For this reason, our control group comprised patients treated with ondansetron only.

Dexamethasone is a high-potency, long-acting glucocorticoid with good bioavailability and few corticoid-related adverse effects(16). Glucocorticoids reduce PONV through a central antiemetic effect by inhibiting

prostaglandin synthesis and release of endogenous opioids(17). Another reason for the antiemetic effect of dexamethasone is the anti-inflammatory response that inhibits the release and reduces the levels of inflammatory factors such as C-reactive protein and interleukin-6(8–10). Our research team systematically explored the potential clinical benefit of multiple low doses of dexamethasone, including two or three doses in the setting of total hip and knee arthroplasty(8–10, 18). In studies performed by Xu et al.(8)and Lei et al.(9), two doses of 10 mg dexamethasone were intravenously administered upon anesthetic induction and return to the inpatient unit. Two other studies by the same research teams evaluated the efficacy and safety of three doses of dexamethasone (10 or 20 mg at anesthetic induction, 10 mg after returning to the inpatient unit, and 10 mg at 24 hours after the first dose) following primary total hip and knee arthroplasty(10, 18). In all of the aforementioned studies, the authors focused on the effect of dexamethasone on the postoperative inflammatory response, pain relief, and joint function. All studies also indicated promising effects of three doses of dexamethasone. In contrast to these previous studies, the current study mainly focused on the outcomes of PONV, appetite, bowel function, and safety. Moreover, the prophylactic regimen in the current study was different from that in the previous studies; i.e., the current regimen combined dexamethasone with a 5-$HT_4$ agonist at different time intervals instead of a 5-$HT_3$ antagonist. Additionally, we compared the new regimen with other common regimens (ondansetron only and a single dose of dexamethasone). This is a major strength of our study.

Another advantage of dexamethasone for PONV prevention is the additional anti-inflammatory effect. A previous study demonstrated that PONV is specific to the patients' perioperative inflammatory control [20]. Systematic reviews and meta-analyses have also shown that a high dose of dexamethasone (≥10 mg or ≥0.1 mg/kg) more effectively reduces the incidence of PONV and provides better postoperative pain control(19, 20). Similar to another study(21), our preliminary results indicated that most of the PONV episodes (87%) occurred during the first 12 hours postoperatively. Therefore, we hypothesized that multiple doses would be more effective. Our results also revealed a lower incidence of severe PONV (1.72%) and a shorter duration (< 6 h) in the patients treated with three doses of dexamethasone. Moreover, the patients in this group (Group C) experienced better pain control with respect to less opioid consumption (Table 5), and this also contributed to the lower incidence of PONV.

Mosapride, a 5-$HT_4$ receptor agonist, is a gastroprokinetic agent indicated for the treatment of gastrointestinal symptoms such as heartburn, nausea/vomiting associated with chronic gastritis, and functional dyspepsia(11). The in vivo study by Mine et al.(22) showed that mosapride was helpful to improve the selective serotonin reuptake inhibitor (SSRI)-induced delay in gastric emptying and the incidence of SSRI-induced emesis, which was in accordance with another clinical study(23). Moreover, another study also showed the potential anti-emetic effect of mosapride in patients undergoing chemotherapy(12). Interestingly, in the present study, the patients in Group B (oral mosapride in addition to a single dose of dexamethasone) had a lower incidence of PONV (although not significantly lower) during the first 6 hours. Additionally, a shorter duration of time passed until the first defecation. This raises the possibility that oral mosapride is helpful to reduce the incidence of PONV by promoting gastrointestinal motility. Although our results indicated no adverse events such as prolonged QT

syndrome associated with mosapride, in view of the fact that another 5-$HT_4$ receptor agonist, cisapride, was withdrawn because of severe cardiotoxicity, further studies are warranted to investigate the potential antiemetic efficacy and safety profile of mosapride in the setting of joint arthroplasty before routine recommendation.

In addition to the fewer episodes and decreased severity of PONV in Group C, these patients had better bowel function, higher appetite scores, shorter hospital stays, and higher satisfaction scores. This might have been partially due to the application of mosapride, although multiple doses of dexamethasone could have improved the pain control, joint function, early ambulation, and length of hospital stay.

The main obstacle to the widespread application of dexamethasone is the concern about its safety, especially in terms of the risk of infection and hyperglycemia. Although the literature has provided some evidence that the use of low-dose dexamethasone does not increase the risk of adverse events(24, 25), the current results were inconclusive. In our study, the fasting blood glucose level in patients both with and without diabetes receiving dexamethasone significantly increased, but it remained at an acceptable level. Additionally, the incidence of wound complications during the follow-up period was comparable among the three groups. Nevertheless, we cannot conclude that the use of dexamethasone is safe because our study sample was not large enough to detect statistical significance. A previous power analysis showed that > 3500 patients would be required to meaningfully evaluate an increase in surgical infection(19). Thus, we must acknowledge that this study lacks the power to fully assess the low incidence of events because of the relatively small sample size. The rate of such negative outcomes could be much more severe than what we expected, and the results should be interpreted with caution. Although large-scale prospective studies are still needed, our study might provide some insight into the safety of dexamethasone.

We acknowledge that our study has some limitations. First and foremost, the generalizability of this regimen was limited because of same postoperative pain management and anesthesia protocol. Different from most western countries, general anesthesia was preferable by the anesthesia team in our institution because of better feasibility of early ambulation and anticoagulation. Second, we did not evaluate the effect of this regimen on the postoperative inflammatory response and other functional outcomes because previous studies have confirmed its efficacy in this regard(8–10). Finally, the follow-up period was too short to detect the possible infectious complications associated with dexamethasone. Despite these limitations, this was a prospective randomized controlled trial with calculation of the sample size before study commencement. In addition, all operations were performed with standardized anesthetic and surgical protocols.

# Conclusion

Prophylactic use of mosapride and three doses of dexamethasone effectively reduced the incidence of PONV. Additionally, this regimen resulted in a better postoperative appetite, bowel function recovery, and

pain relief when compared with a single dose or ondansetron only in patients undergoing primary total joint arthroplasty under general anesthesia.

# Abbreviations

PONV, postoperative nausea and vomiting; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists; PACU, post-anesthesia care unit; BMI, body mass index.

# Declarations

### *Ethics approval and consent to participate*

The study protocol was approved by the Institutional Review Board of West China Hospital, Sichuan University (2012-268), and all procedures were performed according to the Declaration of Helsinki. Written informed consent was obtained prospectively from all patients prior to surgery.

### *Consent for publication*

Not applicable

### *Availability of data and materials*

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

### *Competing interests*

The authors declare that they have no competing interests.


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### *Authors' contributions*

Conceptualization, Z. Zhou and F. Pei; Methodology, J. Xie and Y. Cai; Formal analysis, J. Ma and Q. Huang; Investigation, Y. Cai and J. Xie; Resources, Z. Zhou and F. Pei; Data curation and Writing, Y. Cai and J. Xie; Project administration and Funding Acquisition, F. Pei and J. Xie.


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# Tables

**Table 1.** Baseline characteristics of all patients

| | Group A (n= 108) | Group B (n= 108) | Group C (n= 116) | p value |
|---|---|---|---|---|
| Age (years) | 57.41±14.20 | 62.21±12.68 | 61.17±13.31 | .087 |
| BMI (kg/m$^2$) | 23.86±4.05 | 24.11±3.23 | 24.14±3.88 | .899 |
| Female / Male | 74 / 34 | 75 / 33 | 80 / 36 | .993 |
| Smoking (n, %) | 34 (31.48%) | 35 (32.41%) | 22 (18.20%) | .164 |
| History of kinetia | | | | .506 |
| YES | 44 | 42 | 36 | |
| NO | 64 | 66 | 80 | |
| ASA Score | | | | .813 |
| ASA=2 | 76 | 75 | 86 | |
| ASA=3 | 32 | 33 | 30 | |
| Type of surgery | | | | |
| THA | 52 | 45 | 64 | .245 |
| TKA | 56 | 63 | 52 | |
| Number of comorbidities | | | | .518 |
| 1 | 42 | 52 | 50 | |
| ≥2 | 8 | 12 | 14 | |
| Operation time (min) | 77.35±20.885 | 77.66±26.158 | 78.34±19.304 | .973 |
| Anesthesia time (min) | 126.72±28.69 | 123.87±31.143 | 122.12±21.982 | .688 |
| PACU time (min) | 72.72±47.353 | 78.03±38.907 | 75.03±35.992 | .72 |
| Sufentanil (mg) | 24.31±3.36 | 24.63±3.32 | 24.59±5.60 | .888 |
| Remifentanil (mg) | 0.588±0.145 | 0.624±0.245 | 0.636±0.2723 | .530 |
| Propofol (mg) | 202.75±109.4 | 206±129.9 | 225±122.064 | .565 |
| Midazolam (mg) | 2.09±0.46 | 2.13±0.482 | 2.33±0.839 | .059 |
| Atracurium (mg) | 13.57±2.568 | 13.89±2.955 | 13.32±3.766 | .511 |
| Sevoflurane (ml) | 30.809±6.628 | 30.2±9.521 | 28.622±7.168 | .341 |

ASA, American Society of Anesthesiologists; BMI, body mass index; THA, total hip arthroplasty; TKA, total knee arthroplasty; PACU, post-anesthesia care unit.

**Table 2.** Incidence of PONV during the first postoperative 48 hours

| | Group A (n= 108) | Group B ( n= 108) | Group C (n= 116) | P* | p1† | p2† | p3† |
|---|---|---|---|---|---|---|---|
| Nausea | 34 (31.48%) | 23 (21.30%) | 18 (15.52%) | .016 | .086 | **.005** | .264 |
| Vomiting | 22 (20.37%) | 17 (15.74%) | 16 (13.79%) | .401 | - | - | - |
| Mild PONV | 4 (3.70%) | 2 (1.85%) | 8 (6.90%) | .176 | - | - | - |
| Moderate PONV | 10 (9.26%) | 7 (6.48%) | 8 (6.90%) | .763 | - | - | - |
| Severe PONV | 20 (18.52%) | 14 (12.96%) | 2 (1.72%) | <.001 | .262 | **<.001** | **.001** |
| Mild+ severe PONV | 30 (27.78%) | 21 (19.44%) | 10 (8.62%) | .001 | .149 | **<.001** | **.019** |
| Complete response | 52 (48.15%) | 68 (62.96%) | 82 (70.69%) | .002 | .028 | **.001** | .219 |

Data are presented as number of patients (percentage).
PONV, postoperative nausea and vomiting
*Uncorrected p values (for the three-way comparison)
†Bonferroni-corrected p values: p1, Group A vs. B; p2, Group A vs. C; p3, Group B vs. C. The corrected significance threshold was 0.016.

**Table 3.** Timing of PONV events during the postoperative period

| Time | Total (n= 332) | Group A (n= 108) | Group B ( n= 108) | Group C (n= 116) | p* | p1† | p2† | p3† |
|---|---|---|---|---|---|---|---|---|
| 0 – 6 h | 52 (69.33%) | 16 (47.06%) | 19 (82.61%) | 17 (94.44%) | .001 | **.007** | **.001** | .363 |
| 6 – 12 h | 9 (12%) | 6 (17.65%) | 2 (8.70%) | 1(0.56%) | .106 | - | - | - |
| 12 – 24 h | 7 (9.33%) | 6 (17.65%) | 1 (4.35%) | 0 | .006 | .119 | **.012** | .482 |
| 24 – 48 h | 7 (9.33%) | 6 (17.65%) | 1 (4.35%) | 0 | .006 | .119 | **.012** | .482 |

Data are presented as number of patients (percentage).
PONV, postoperative nausea and vomiting
*Uncorrected p values (for the three-way comparison)
†Bonferroni-corrected p values: p1, Group A vs. B; p2, Group A vs. C; p3, Group B vs. C. The corrected significance threshold was 0.016.

**Table 4.** Duration of PONV during the first postoperative 48 hours

| Duration | Total (n= 332) | Group A (n= 108) | Group B ( n= 108) | Group C (n= 116) | p* | p1† | p2† | p3† |
|---|---|---|---|---|---|---|---|---|
| Mean time (h) | 13.6±15.37 | 16.18±14.95 | 18.17±18.20 | 2.89±1.71 | .002 | .606 | .002 | .001 |
| < 6 h | 37 (49.33%) | 12 (35.29%) | 9 (39.13%) | 16 (88.89%) | .001 | .768 | **<.001** | **.001** |
| 6 -12 h | 14 (18.67%) | 8 (23.53%) | 4 (17.39%) | 2 (11.11%) | .610 | - | - | - |
| 12-24 h | 8 (10.67%) | 4 (11.76%) | 4 (17.39%) | 0 | .189 | - | - | - |
| > 24 h | 16 (21.33%) | 10 (29.41%) | 6 (26.09%) | 0 | .039 | .784 | .010 | .027 |

Data are presented as number of patients (percentage) or mean ± standard deviation.
PONV, postoperative nausea and vomiting
*Uncorrected p values (for the three-way comparison)
†Bonferroni-corrected p values: p1, Group A vs. B; p2, Group A vs. C; p3, Group B vs. C. The corrected significance threshold was 0.016.

**Table 5.** Requirement of rescue treatment for PONV and pain during the postoperative 48h

| | Group A (n= 108) | Group B (n= 108) | Group C (n= 116) | p* | p1† | p2† | p3† |
|---|---|---|---|---|---|---|---|
| Metoclopramide (mg) | 6.48±19.148 | 2.87±8.209 | 1.38±3.478 | .047 | .055 | **.017** | .415 |
| Ondansetron (mg) | 0.52±1.746 | 0.48±1.705 | 0.1±0.583 | .238 | - | - | - |
| Oxycodone (mg) | 33.2±38.7 | 17.9±29.7 | 0.3±1.8 | <.001 | .001 | **<.001** | **<.001** |
| Pethidine (mg) | 20.4±28.3 | 20.6±29.8 | 6.0±1.0 | .002 | .959 | **.005** | **.001** |

Data are presented as mean ± standard deviation.

PONV, postoperative nausea and vomiting

*p values with one-way analysis of variance; †p values with Tukey;s post hoc test.

P1, Group A vs. B; p2, Group A vs. C; p3, Group B vs. C.

**Table 6.** Other clinical outcomes

| | Group A (n= 108) | Group B (n= 108) | Group C (n= 116) | p | p1 | p2 | p3 |
|---|---|---|---|---|---|---|---|
| Time to first defecation (h) | 52.43±16.48 | 46.67±11.79 | 37.2±8.97 | <.001 | **.006** | **<.001** | **<.001** |
| Appetite score on POD 0 | 2.19±0.754 | 2.37±0.678 | 2.59±0.622 | .009 | .106 | .002 | .054 |
| Appetite score on POD 1 | 2.3±0.69 | 2.41±0.684 | 2.74±0.48 | .001 | .298 | **<.001** | **.002** |
| Appetite score on POD 2 | 2.57±0.536 | 2.58±0.532 | 2.74±0.442 | .121 | - | - | - |
| Time to first ambulation (h) | 27.09±8.225 | 28.45±10.79 | 25.63±6.299 | .298 | - | - | - |
| Satisfaction score | 9.31±0.747 | 9.26±0.912 | 9.72±0.433 | .001 | .661 | **.007** | **<.001** |
| LOH (d) | 5.37±2.113 | 5.04±2.157 | 4.1±2.157 | .02 | .321 | **.001** | **.049** |

Data are presented as mean ± standard deviation.

POD, postoperative day; LOH, length of hospitalization.

P1, Group A vs. B; p2, Group A vs. C; p3, Group B vs. C.

**Table 7.** Incidence of complications and level of blood glucose on POD 1 and 2

| | Group A (n= 108) | Group B ( n= 108) | Group C (n= 116) | p* | p1† | p2† | p3† |
|---|---|---|---|---|---|---|---|
| Diabetes Mellitus patients | | | | | | | |
| FBG on POD1 | 9.46±2.17 | 10.73±2.36 | 11.00±2.92 | .001 | .001 | **.001** | .525 |
| 2-h PBG after breakfast | 11.58±1.53 | 12.29±3.08 | 14.85±3.87 | .002 | .177 | **.001** | **.001** |
| 2-h PBG after lunch | 11.53±1.25 | 13.17±3.73 | 14.80±2.64 | .096 | - | - | - |
| 2-h PBG after dinner | 10.98±2.28 | 12.65±3.22 | 10.12±2.72 | .173 | - | - | - |
| FBG on POD2 | 9.43±0.99 | 9.77±2.11 | 7.68±3.11 | .127 | - | - | - |
| Non- Diabetes Mellitus patients | | | | | | | |
| FBG on POD1 | 6.77±1.21 | 6.91±1.59 | 7.80±1.27 | .021 | .212 | **.017** | **.041** |
| FBG on POD2 | 5.55±1.03 | 5.67±1.83 | 7.06±1.24 | .031 | .76 | **.039** | **.048** |
| Prolonged QT syndrome | 0 | 0 | 0 | - | | | |
| Wound site discharge | 2 (1.85%) | 3 (2.78%) | 4 (3.45) | .913 | - | - | - |
| Surgical site infection | 0 | 0 | 0 | - | | | |
| Pulmonary infection | 2 (1.85%) | 6 (5.56%) | 1 (0.86%) | .104 | - | - | - |
| Re-admission | 1 (0.93%) | 1 (0.93%) | 1 (0.86%) | 1.000 | - | - | - |

Data are presented as mean ± standard deviation or number (percentage).
POD, postoperative day; FBG, fasting blood glucose; PBG, 2-hour postprandial blood glucose.
*p values with one-way analysis of variance; †p values with Tukey's post hoc test.
p1, Group A vs. B; p2, Group A vs. C; p3, Group B vs. C.

# Figures

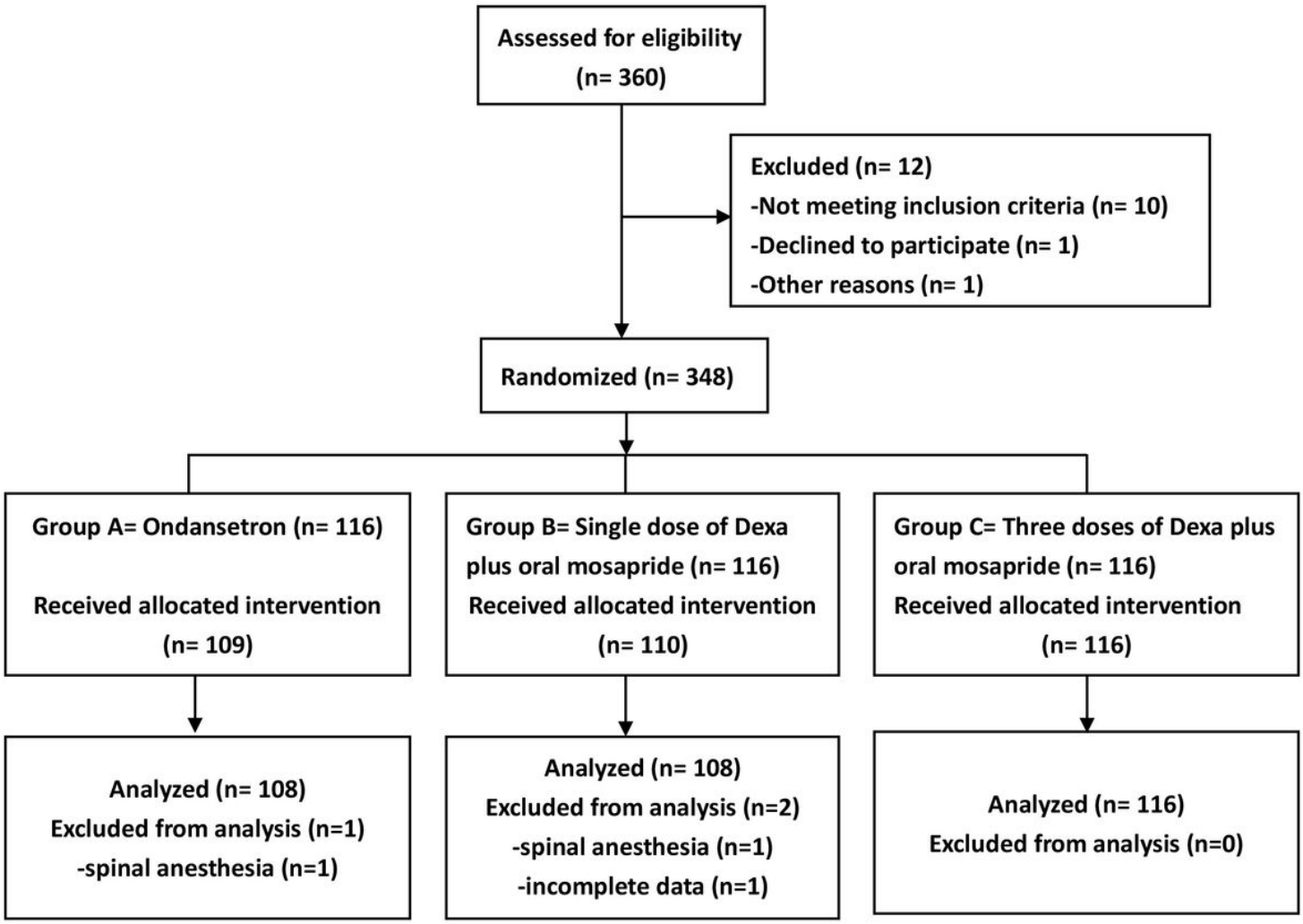


**Figure 1**

A flow diagram shows the patients recruitment.