

## Clinical Efficacy of Sub-hypnotic Dose of Propofol and Ondansetron for Postoperative Nausea and Vomiting Prophylaxis in TKA or THR surgery: a Non-inferiority Trial

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### Abstract

**Background:** Postoperative nausea and vomiting (PONV) is one of the most common and unpleasant symptoms affecting patients undergoing total knee arthroplasty (TKA) or total hip replacement (THR) surgery under spinal anesthesia with intrathecal morphine. It is a dreadful and uncomfortable experience that significantly detracts patients' quality of life after surgery.

**Objective:** This study was to assess the effect of a sub hypnotic dose of propofol on the incidence and severity of PONV after TKA or THR surgery.

**Methods:** 144 patients presenting for elective TKA and THR surgery at Maharat Nakhon Rachasima Hospital were recruited. Each patient was randomly assigned to two groups; Propofol group (n=72) received propofol 20 mg and ondansetron group (n=72) received ondansetron 8 mg IV slowly push 15 minutes after spinal

anesthesia. Spinal anesthesia was performed using 0.5% hyperbaric or isobaric bupivacaine 12-16 mg with 0.2 mg intrathecal morphine. The episodes and severity of PONV during the first 24 h after anesthesia were evaluated.

**Results:** Percentages of PONV after TKA and THR surgery under spinal anesthesia with intrathecal morphine of propofol group and ondansetron group were 30.6% and 37.5%, respectively. There was no significant difference between the two groups ( $P=0.84$ ). There were no significant differences between the groups regarding to the hemodynamic parameters and sedative effects.

**Conclusion:** Sub-hypnotic dose of propofol offers a PONV prophylaxis for patients undergoing TKA and THR surgery under spinal anesthesia with intrathecal morphine non-inferiorly to PONV prophylaxis with ondansetron.

**Keywords:** antiemetic, intrathecal morphine, postoperative nausea and vomiting, propofol, total hip replacement, total knee arthroplasty

## Introduction

Maharat Nakhon Ratchasima Hospital is a large regional hospital under the responsibility of the Ministry of Public Health. Each year, a significant number of patients undergo total knee arthroplasty (TKA) and total hip replacement (THR) surgeries at the hospital.<sup>1</sup> The use of spinal anesthesia in combination with intrathecal morphine is the most common anesthetic technique employed in TKA and THR surgeries, owing to the fact that it is easy to perform and provides a fast surgical block and effective pain relief after surgery.<sup>2,3</sup> Nevertheless, major side effects of the foregoing technique include postoperative nausea and vomiting (PONV) and pruritus<sup>4</sup>, which subsequently lead to delayed postoperative recovery, prolonged hospitalization, high costs of hospital care, and low level of patient satisfaction with anesthesia and surgery care.<sup>5,6</sup>

Considering the fact that the pathology of PONV involves multiple pathways and risk factors, a variety of antiemetics have been developed for treatment of PONV, each of which has different mechanisms of action. Despite the widespread availability of antiemetics, prevention is regarded as the best approach for management of PONV.<sup>5</sup> The majority of antiemetics, such as ondansetron, droperidol, and metoclopramide, are accompanied by several side effects, namely constipation, arrhythmia, prolonged QT interval, agitation, extrapyramidal syndrome, and dystonic reactions.<sup>7</sup> Propofol is one of the most widely used intravenous anesthetic agents for induction and maintenance of anesthesia. The findings of previous studies suggest that sub-hypnotic doses of propofol are effective in the prevention of

nausea and vomiting following the administration of spinal anesthesia with intrathecal morphine.<sup>7</sup> Although the mechanism of action for propofol is not clearly understood, it is believed to involve the inhibition of serotonin (5-HT<sub>3</sub>) receptors.<sup>8,9</sup> Apart from PONV, another common side effect of intrathecal morphine in spinal anesthesia is pruritus, which occurs in 60-70% of patients. Previous studies found that ondansetron and propofol are effective in the treatment of intrathecal morphine-induced pruritus.<sup>8,10</sup>

The approach adopted by Maharat Nakhon Ratchasima Hospital for prevention of PONV in patients receiving spinal anesthesia and intrathecal morphine during TKA and THR surgeries includes the administration of ondansetron in combination with chlorpheniramine. However, ondansetron must be carefully administered to patients due to its side effects. The purpose of this study was to compare the antiemetic efficacy of a sub-hypnotic dose of propofol with ondansetron for the prevention of PONV and pruritus in patients receiving intrathecal morphine during TKA and THR surgeries.

## Methods

The study was approved by an Institutional Ethics Committee of Maharat Nakhon Ratchasima Hospital. This study has been done from 2018 to 2020 in Maharat Nakhon Ratchasima Hospital.

## Subjects

This study was a randomized controlled trial and recruited 144 patients. The participants were enrolled from the patients that were

scheduled for TKA (primary and revision) or THR (primary and revision) under spinal anesthesia with intrathecal morphine. The inclusion criteria were age 20 to 75 years old and ASA classification I-II. The exclusion criteria were as follows: patients who did not give consent, relevant drug allergy, motion sickness, contraindications for spinal anesthesia, conversion from spinal anesthesia to general anesthesia. After the patients signed the informed consent, they were divided into two groups by the random sequence generated by computer (propofol and ondansetron groups).

### Randomization

The patients were randomly assigned to one of two groups using a computer-generated random number table. Propofol group (n=72) received intravenous propofol 20 mg and ondansetron group (n=72) received intravenous ondansetron 8 mg.

### Anesthesia induction and drug application

All patients were prospectively assessed for the basic monitoring (ECG, SpO<sub>2</sub>, and non-invasive blood pressure) and the baseline vital signs were checked and recorded. After positioning the patient in lateral position, spinal anesthesia was performed at the level of L3-L4 or L4-L5 space through a midline approach. The subarachnoid block was then established with 12-16 mg hyperbaric or isobaric bupivacaine, and 0.2 mg morphine. The patient was then asked to return to the supine position. Following confirmation of sensory block by loss of

sensation to cold and pinprick level, ECG, SpO<sub>2</sub>, pulse rate, respiratory rate and arterial blood pressure were monitored and recorded. The decrease in systolic blood pressure (more than 20% from baseline values and/or less than 90 mmHg) after spinal injection was treated by increasing the rate of intravenous fluid administration and 5-10 mg increments of ephedrine administered intravenously. Patients were randomly assigned into one of the two groups (n=72 each) using a computer-generated randomization chart to receive either an intravenous injection of propofol at a sub-hypnotic dose (20 mg) or ondansetron (8 mg) at 15 min after spinal anesthesia.

### Measurements

The incidence of PONV was recorded hourly for the first 4 hours and then every 4 hours for the next 24 hours at ward. Nausea and vomiting were assessed using Bellville scoring tools (0=no symptoms, 1=nausea, 2=retching, 3=vomiting).<sup>11</sup> Postoperative rescue antiemetic was metoclopramide 10 mg intravenous injection if Bellville score is 3. The incidence of pruritus was recorded every 4 h for 24 h after surgery on a four-point categorical scale as; 0=no pruritus, 1=mild, 2=moderate and 3=severe pruritus. The incidence of sedation was recorded every 4 h for 24 h after surgery on a four-point categorical scale as; 0=none, 1=mild, 2=moderate and 3=severe during the postoperative follow-up. Chlorpheniramine 10 mg was administered if pruritus ensues or on request and Naloxone hydrochloride 2 mcg/kg was injected to manage opioid-induced respiratory depression. Hemody-

hemic variables including pulse rate, NIBP, SpO<sub>2</sub>, and respiratory rate were recorded before and after the administration of propofol or ondansetron, and were followed for 24 h postoperatively. Primary outcome compared the incidence and severity of postoperative nausea and vomiting in patients under spinal anesthesia with intrathecal morphine for 24 hours between doses of propofol with ondansetron. Secondary outcome compared the incidence of pruritus in patients under spinal anesthesia with intrathecal morphine for 24 hours between doses of Propofol with Ondansetron. As a double-blinded study, the induction of spinal anesthesia and intravenous injection of propofol or ondansetron were performed by the authors while the incidence of PONV record was performed, and other complications were recorded by the nurse anesthetist.

### Statistical analysis

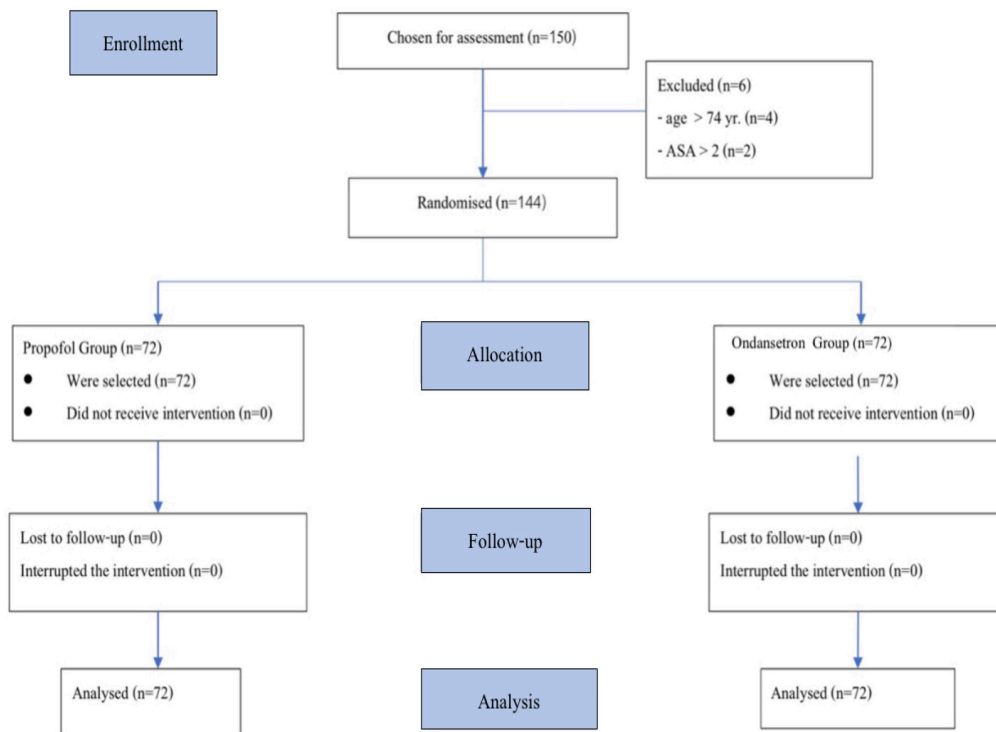
Analysis STATA 15 for Windows was used to analyze all data in this study. The sample size was calculated based on the data from the pilot study (20 cases/group). The non-inferiority analysis (power = 80% and  $\alpha = 0.1$ )<sup>12</sup> was used to compare the proportion of patients experiencing PONV, with was primary outcome between Group propofol (P1=57.4%) and Group ondansetron (P2=80.0%) in patients undergoing TKA and THR surgery under spinal anesthesia with intrathecal morphine. This resulted in a total of 144 subjects needed. Continuous variables were presented as median and interquartile range for non-normally distributed data or mean and standard deviation for normally distributed data. Categorical variables

were compared using Pearson's Chi-square test. T-test was used for statistical comparisons for normally distributed continuous variables (hemodynamic change) and Mann-Whitney U test was used for non-normally distributed data. A  $P < 0.05$  was considered statistically significant.

### Results

The total number of patients that were scheduled for TKA and THR during the study period was 150, out of which 6 patients were excluded. The remaining 144 participants completed the trial. All patients were randomized into propofol and ondansetron groups (Figure 1). The results indicated that both groups had a similar demographic profile in terms of age, gender, weight, and ASA classification (Table 1). According to Table 2 which presents anesthesia and surgery information, there was no significant difference between the two groups in respect of anesthetic depth, duration of surgery, and duration of anesthesia. All patients had an adequate sensory level of spinal block for surgery, i.e., T6-T12 sensory level. There were no differences between the two groups ( $P=0.81$ ).

With regard to the outcomes of patients during the first 24 hours after surgery, there was no significant difference in the incidence and severity of PONV between the two groups ( $P=0.84$ ). Specifically, 22 (30.6%) cases of PONV were found in the propofol group and 27 (37.5%) cases were found in the ondansetron group. The proportion of patients treated with antiemetics was not significantly different between the two groups (4.2% in propofol group, 5.6% in



**Figure 1** Consort flow diagram

**Table 1** Demographics data

| Characteristics                          | Propofol (n=72) | Ondansetron (n=72) | P-value |
|------------------------------------------|-----------------|--------------------|---------|
| <b>Sex (n, %)</b>                        |                 |                    | 0.61    |
| Male                                     | 10 (13.9)       | 8 (11.1)           |         |
| Female                                   | 62 (86.1)       | 64 (88.9)          |         |
| <b>Age, yr (mean, SD)</b>                | 59.6 (6.8)      | 59.9 (6.6)         | 0.80    |
| <b>ASA Classification (n, %)</b>         |                 |                    | 0.83    |
| ASA I                                    | 14 (19.4)       | 59 (81.9)          |         |
| ASA II                                   | 58 (80.6)       | 13 (18.1)          |         |
| <b>Underlying disease (n, %)</b>         |                 |                    | 0.69    |
| Diabetes mellitus                        | 27 (37.5)       | 27 (37.5)          |         |
| Hypertension                             | 20 (27.7)       | 25 (34.7)          |         |
| Diabetes mellitus and hypertension       | 11 (15.4)       | 7 (9.7)            |         |
| <b>Weight (kg) (mean, SD)</b>            | 65.8 (7.8)      | 65.2 (7.7)         | 0.70    |
| <b>BMI (kg/m<sup>2</sup>) (mean, SD)</b> | 26.6 (3.1)      | 26.8 (2.8)         | 0.57    |

**Table 2** Intraoperative data

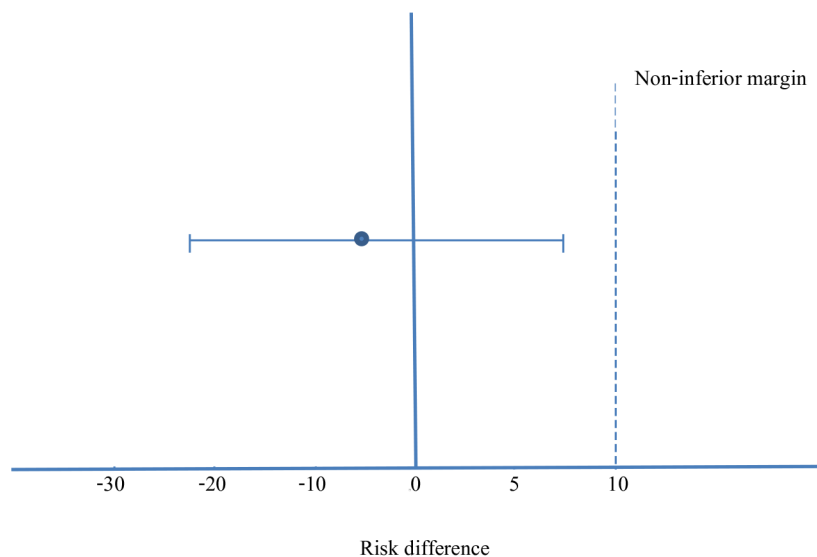
| Characteristics                                                       | Propofol (n=72) | Ondansetron (n=72) | P-value |
|-----------------------------------------------------------------------|-----------------|--------------------|---------|
| <b>Type of operation (n, %)</b>                                       |                 |                    | 0.64    |
| TKA                                                                   | 60 (83.3)       | 62 (86.1)          |         |
| THR                                                                   | 12 (16.7)       | 10 (13.9)          |         |
| <b>Anesthetic agent (n, %)</b>                                        |                 |                    | 0.56    |
| Hyperbaric bupivacaine                                                | 52 (72.3)       | 55 (76.4)          |         |
| Isobaric bupivacaine                                                  | 20 (27.7)       | 17 (23.6)          |         |
| <b>Volume of bupivacaine, mL (mean, SD)</b>                           | 2.9 (0.2)       | 2.9 (0.1)          | 0.20    |
| <b>Level of anesthesia (n, %)</b>                                     |                 |                    | 0.81    |
| T6                                                                    | 7 (9.7)         | 9 (12.5)           |         |
| T8                                                                    | 20 (27.8)       | 22 (30.6)          |         |
| T10                                                                   | 37 (51.4)       | 31 (38.9)          |         |
| T12                                                                   | 8 (11.1)        | 10 (13.9)          |         |
| <b>Duration of anesthesia, min (mean, SD)</b>                         | 113.7 (13.7)    | 112.9 (11.4)       | 0.72    |
| <b>Duration of surgery, min (mean, SD)</b>                            | 73.1 (8.9)      | 74.2 (7.2)         | 0.42    |
| <b>Estimated blood loss, mL (median, IQR)</b>                         | 50.0 (30.0)     | 50.0 (10.0)        | 0.54    |
| <b>Mean arterial pressure, mmHg (mean, SD)</b>                        |                 |                    |         |
| Before anesthesia                                                     | 96.9 (7.4)      | 95.5 (6.1)         | 0.13    |
| After anesthesia                                                      | 89.2 (6.8)      | 87.4 (5.2)         | 0.08    |
| After drug administration                                             | 83.4 (7.9)      | 82.6 (5.0)         | 0.40    |
| <b>Patients who received ephedrine after spinal anesthesia (n, %)</b> | 2 (2.8)         | 2 (2.8)            | 1.00    |

ondansetron group,  $P=0.70$ , Table 3 and Figure 2). Although the incidence of pruritus in the propofol group (30.6%) was less than in the ondansetron group (44.4%), there was no statistically significant difference ( $P=0.21$ ). Regarding the changes in mean arterial pressure (MAP) before, after anes-

thesia and after drug administration, there was no statistically significant difference between the propofol group and the ondansetron group ( $P=0.13$ , 0.08 and 0.46, respectively, Table 2). After induction of anesthesia, two patients in each group (7.8%,  $P=1.00$ ) were found hypotensive and

**Table 3** Incidence and severity of postoperative nausea and vomiting

|                                                    | Propofol<br>(n=72) | Ondansetron<br>(n=72) | P-value | Risk/Mean<br>difference/<br>(95% CI) |
|----------------------------------------------------|--------------------|-----------------------|---------|--------------------------------------|
| Nausea vomiting score (n, %)                       |                    |                       | 0.84    | -6.9%                                |
| No symptoms                                        | 50 (69.4)          | 45 (62.5)             | 0.38    | (-22.4%,8.5%)                        |
| Nausea                                             | 13 (18.1)          | 15 (20.8)             | 0.67    |                                      |
| Retching                                           | 6 (8.3)            | 8 (11.1)              | 0.57    |                                      |
| Vomiting                                           | 3 (4.2)            | 4 (5.6)               | 0.70    |                                      |
| Nausea and vomiting requiring<br>medication (n, %) | 3 (4.2)            | 4 (5.6)               | 0.70    |                                      |

**Figure 2** Postoperative nausea and vomiting results

required the treatment with ephedrine injection. However, there was no incidence of hypotension after the administration of propofol and ondansetron. In addition, there was no statistically significant difference between the two groups in terms of sedation score ( $P=0.10$ , Table 4).

## Discussion

This study was designed to compare the efficacy of two types of antiemetics. According to the results, the incidence of PONV was found to be 34%, in which there was no statistically

**Table 4** Incidence and severity of postoperative pruritus

|                       | Propofol<br>(n=72) | Ondansetron<br>(n=72) | P-value | Risk Difference/<br>Mean difference<br>(95% CI) |
|-----------------------|--------------------|-----------------------|---------|-------------------------------------------------|
| Pruritus score (n, %) |                    |                       | 0.37    | -13.8%                                          |
| No symptoms           | 50 (69.4)          | 40 (55.6)             |         | (-29.5%,1.8%)                                   |
| Mild                  | 17 (23.7)          | 23 (31.9)             |         |                                                 |
| Moderate              | 3 (4.2)            | 5 (6.9)               |         |                                                 |
| Severe                | 2 (2.8)            | 4 (5.6)               |         |                                                 |

**Table 5** Sedation score

|                       | Propofol<br>(n=72) | Ondansetron<br>(n=72) | P-value |
|-----------------------|--------------------|-----------------------|---------|
| Sedation score (n, %) |                    |                       | 0.10    |
| None                  | 58 (80.6)          | 65 (90.3)             |         |
| Mild                  | 14 (19.4)          | 7 (9.7)               |         |
| Moderate              | 0                  | 0                     |         |
| Severe                | 0                  | 0                     |         |

significant difference between the two groups ( $P=0.84$ ). This result is consistent with the findings of Rosillo-Menesesa and coworkers, which indicated that there was no statistically significant difference between the antiemetic efficacy of propofol and ondansetron.<sup>13</sup> Accordingly, it can be deduced that a sub-hypnotic dose of propofol is as effective as ondansetron in the prevention of PONV in patients receiving spinal anesthesia and intrathecal morphine during TKA and THR surgeries. Moreover, the results of this study confirmed our hypothesis that a sub-hypnotic dose of propofol can be used as an antiemetic

to prevent the incidence of PONV in patients receiving spinal anesthesia and intrathecal morphine during TKA and THR surgeries, and that it has the same antiemetic efficacy as ondansetron. Some variables in this study were controlled across the experimental groups. Specifically, the type of surgery, anesthetic technique, and sensory block level were standardized. Likewise, there were no significant differences in terms of duration of anesthesia, duration of surgery, age, weight, and body mass index between the experimental groups.

Furthermore, the study of Hirmanpour and colleagues suggested that ondansetron and sub-hypnotic dose of propofol are both safe and widely accepted due to their same efficacy in the treatment and prevention of spinal opioid-induced pruritus.<sup>14</sup> Their findings were consistent with the results of this study, in which no statistically significant difference in the incidence of intrathecal morphine-induced pruritus between these two groups. Regarding the changes in MAP and complications after administration of antiemetics, there were not significantly different between the two groups. Particularly, there were no incidences of hypotension and residual sedative effects after administration of propofol.

### Limitation

In our study, we only used a bolus dose of propofol and same dose bolus no attempt was made to compare different doses. Which is not the same as previous research using bolus and infusion dose of propofol in all our patients. This causes the efficacy of propofol may be reduced.

### Conclusion

From the evaluation of the efficacy of the postoperative nausea and vomiting prophylaxis of propofol versus ondansetron in spinal anesthesia with intrathecal morphine for total knee arthroplasty and total hip replacement surgery, it was observed that there was no statistically significant difference between the two drugs. Sub-hypnotic dose of propofol offers a PONV prophylaxis for patients undergoing TKA and THR

surgery under spinal anesthesia with intrathecal morphine non-inferiorly to PONV prophylaxis with ondansetron. However, when choosing a drug, consider the limitation and side effects for individual patient.

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