

# Evaluation of Hypotensive Prevention Effect of Intramuscular Glycopyrrolate in Spinal Anaesthesia of Elderly TURP Patients: A Randomized Control Trial

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## ABSTRACT

**Objective:** Spinal anaesthesia is one of the options for patients who need transurethral resection of the prostate (TURP). However, due to typical patient age, risk factors, and the procedure itself, hemodynamic instability is common and hazardous. Glycopyrrolate, an anticholinergic drug, has been used in many indications, including in hypotensive prevention in caesarean section patients undergoing spinal anaesthesia. The study aims to evaluate the hypotensive prevention effect of the drug in elderly (> 60 years) spinal anaesthesia TURP patients.

**Methods:** A prospective randomized control trial of 62 elderly patients who needed TURP was conducted from December 2019 to January 2020. Exclusion criteria were an American Society of Anesthesiologists classification of more than three, contra-indication for glycopyrrolates, and an inability to take spinal anaesthesia. The primary testing process was administration of 0.2 milligram (mg) intramuscular glycopyrrolate 15 minutes before spinal anaesthesia. Data were collected concurrently with hemodynamic parameters, which were recorded as a baseline and every 5 minutes up to 60 minutes. The analysis was done with both single-measure and repeated-measures analysis.

**Results:** Hypotensive incidence was significantly reduced in the glycopyrrolate group (38.7 vs. 74.2%, p-value=0.01) and showed significantly decreased use of epinephrine [0.2 ( $\pm$ 1.1) vs. 4.55 ( $\pm$ 6.0) mg, p-value<0.01]. Intravenous fluid and vasopressor requirements were also lower. All hemodynamic parameters were higher in the glycopyrrolate group, except heart rate.

**Conclusion:** Intramuscular glycopyrrolate could prevent spinal anaesthesia-related hypotension without a difference in heart rate in elderly TURP patients.

**Keywords:** Glycopyrrolate; hypotensive prevention; TURP; spinal anaesthesia; elderly (Siriraj Med J 2020; 72: 380-385)

## INTRODUCTION

Transurethral resection of the prostate (TURP) is an effective therapeutic procedure for indication of benign prostatic hyperplasia (BPH).<sup>1</sup> Although TURP is technically a less invasive procedure, sometimes lethal events can occur either by the process itself or by patient risk factors. The latter is because BPH usually afflicts elderly

patients.<sup>2</sup> Thus, the choice of anaesthesia is essential. Spinal anaesthesia is an attractive option due to the ability to monitor conscious patients directly. Nevertheless, vital sign instability is a troublesome procedure-related unwanted effect.

Hypotension is a frequent procedure-related hemodynamic change and can lead to many adverse

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consequences, even myocardial ischemia.<sup>3</sup> Sympathetic blockade after induction of spinal anaesthesia, which sequentially decreases systemic vascular resistance and cardiac output, is its pathophysiology.<sup>4-6</sup> Unintended and uncorrected hypotension can cause serious consequences, such as myocardial infarction and even death. Reported hypotensive incidence among ageing patients was 65-75%.<sup>6-8</sup> Several preventive strategies were intravenous fluid administration and vasopressors.<sup>9</sup> Nevertheless, TURP-related volume overload can occur and worsen the condition.<sup>10</sup>

Anticholinergic drugs have been proven to be able to prevent adverse cardiovascular effects and decrease secretion during induction of general anaesthesia.<sup>11</sup> The anticholinergic drug glycopyrrolate has reportedly high activity for these preventive effects.<sup>12</sup> Later studies also showed that giving glycopyrrolate before spinal anaesthesia could prevent hypotension and bradycardia in caesarean section<sup>13,14</sup> and in hip arthroplasty patients.<sup>15</sup> Regarding these beneficial effects, we decided to study this drug in elderly TURP patients to determine whether it can alleviate harmful hemodynamic effects. Previous studies reported increased hemodynamic stability using a combination of neostigmine and glycopyrrolate during the reversal of anaesthesia.<sup>16,17</sup> We, however, excluded patients with cardiovascular diseases because there were also some published arrhythmic consequences of the drug in this group of patients.<sup>18</sup>

## MATERIALS AND METHODS

This study was registered with the Thai Clinical Trial Registry (Identification number: TCTR20191105001) and approved by the Sawanpracharak Hospital ethics committee.

BPH patients, who were indicated as needing TURP, were included if they were more than 60 years old and decided to do spinal anaesthesia on an elective basis between December 2019 and January 2020. Patients were excluded if they had an American Society of Anesthesiologists (ASA) classification of more than three, had glycopyrrolate contra-indications (glaucoma, hyperthyroid, morbid obesity, cardiovascular disease, pulmonary disease, renal or hepatic dysfunction, and neuromuscular disease), or were unable to take spinal anaesthesia.

Eligible patients were randomly allocated in parallel by computer-generated numbers and the allocations were sealed in envelopes after informed consent was obtained. Both actions were done by a non-clinically related official. The envelope content was revealed before the beginning of intervention by another non-

clinically involved investigator. Before spinal anaesthesia was administered in the intervention group (Group G), 0.2 milligrams (mg) of glycopyrrolate was given intramuscularly. The same volume of normal saline was given as a placebo to the control group (Group C). Both sets of injections were prepared by the investigator who opened the envelopes. The anaesthesiologist team that gave and recorded outcomes were blind to the group identity during all of the procedures. The study flow is illustrated in Fig 1.

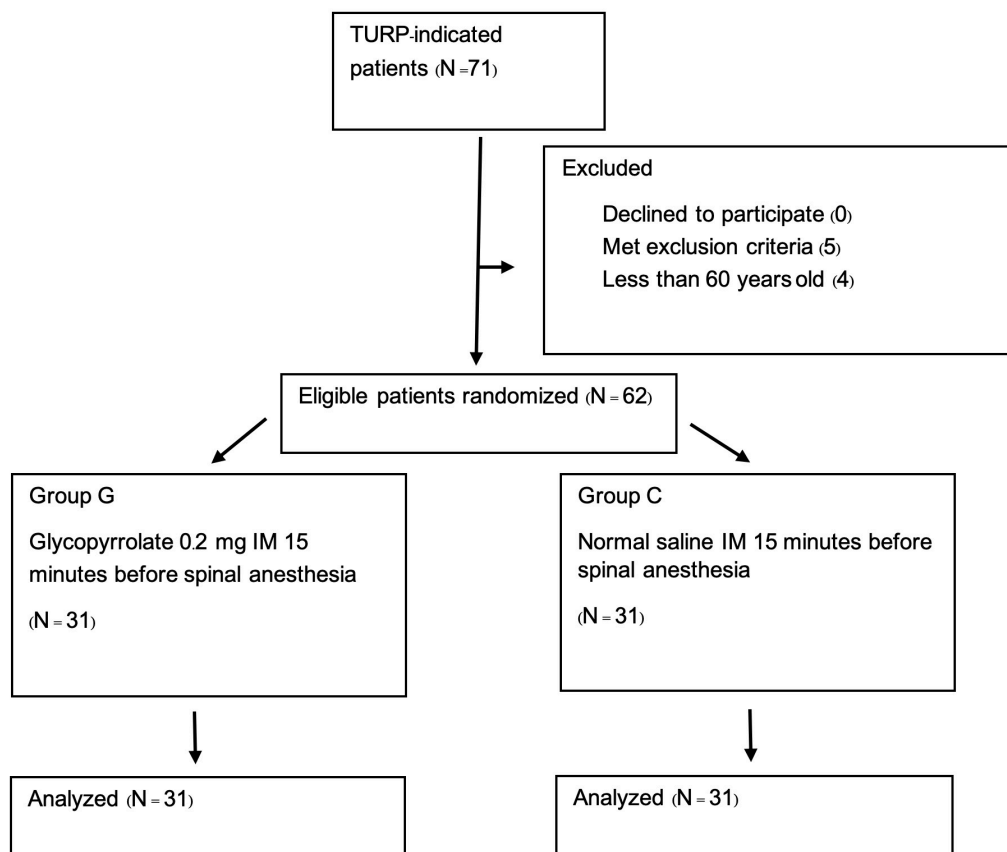
Collected outcomes were age, ASA classification, bupivacaine dosage, spinal blockage level, total ephedrine dosage, total intravenous (IV) volume, estimated blood loss (EBL), and hemodynamic outcomes. The hemodynamic outcomes included systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate. All hemodynamic parameters, which were primary outcomes, were recorded as the baseline, every minute after spinal anaesthesia for 10 minutes, and then every 5 minutes for up to 60 minutes. Hypotension was defined as decreased SBP at least 20% below the patient's baseline level, SBP less than 90 mmHg, or DBP less than 60 mmHg.

Sixty-two of the included participants were calculated to have experienced hypotension: 70% and 27.3% between drug and placebo groups,<sup>15</sup> respectively, with adjusted statistic power to 90% of the two-sided test. Statistical analysis for single-measure data was calculated with Fisher's exact test for categorical data and t-test or Mann-Whitney U test for continuous data. Repeated-measures data were analysed with a multilevel mixed-effects linear regression model. Statistical analysis was performed by statistical software. A p-value of <0.05 was considered to be significant statistically.

## RESULTS

After application of the study design, no eligible patient was excluded, and no patient refused to provide informed consent. Thus, 31 patients were distributed equally in both groups. Table 1 presents the baseline data and the results of single-measure data. Hypotensive incidence was significantly lower in the glycopyrrolate group (38.7 vs. 74.2%, p-value=0.01). With less hypotension, epinephrine use and the IV volume was also lower in the glycopyrrolate group [0.2 ( $\pm$ 1.1) vs. 4.55 ( $\pm$ 6.0) mg, p-value<0.01, and 1.0 ( $\pm$ 0.2) vs. 1.1 ( $\pm$ 0.3) litre, p-value=0.03].

Regarding repeated-measures data, bar graphs with standard error are illustrated in Fig 2, and the summary of statistical analysis results is given in Table 2. The glycopyrrolate group had significantly higher values for all blood pressure parameters. SBP, DBP, and MAP were



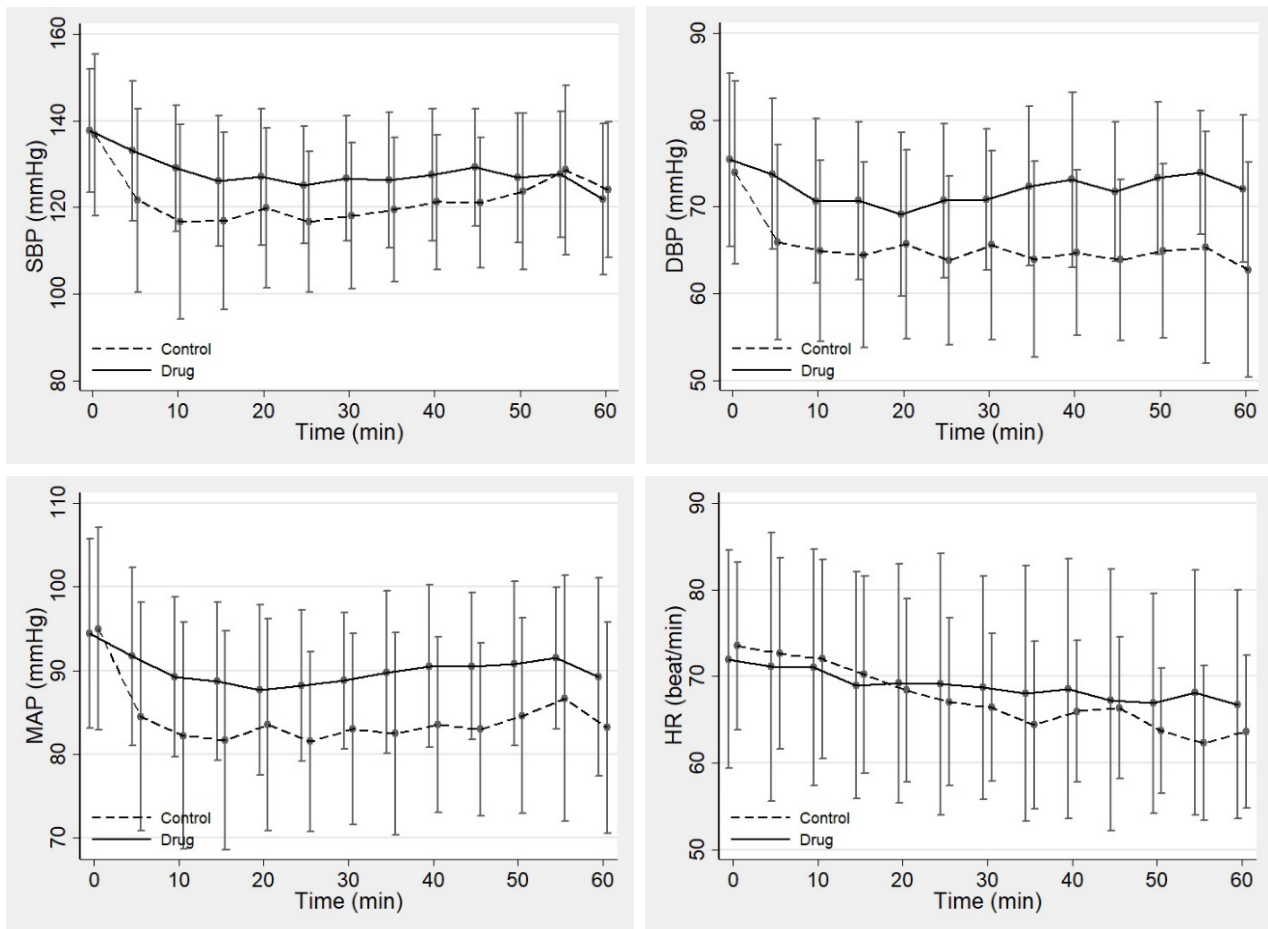
**Fig 1.** Study flow in which 62 patients were assessed for eligibility and eligible subjects were randomized.

**Abbreviations:** Group G = glycopyrrolate group; Group C = control group; IM = intramuscular

**TABLE 1.** Baseline data and single-measure outcomes according to study group.

| Characteristic                                     | Group C         | Group G         | P-value |
|--|-----------------|-----------------|---------|
| Age (years), Mean ( $\pm$ SD)                      | 69.68 (6.5)     | 70.9 (8.0)      | 0.97    |
| Bupivacaine dosage (mg),<br>Median (Range)         | 2.8 (2.6-3.2)   | 2.8 (2.6-4)     | 0.42    |
| Anaesthesia level, N (%)                           |                 |                 |         |
| T6   | 11 (35.5)       | 5 (16.1)        | 0.24    |
| T8   | 9 (29.0)        | 10 (32.3)       |         |
| T10  | 11 (35.5)       | 16 (51.6)       |         |
| Operative time, Median (Range)                     | 30 (25-55)      | 40 (25-85)      | 0.01    |
| EBL (ml), Median (Range)                           | 50 (20-150)     | 50 (20-100)     | 0.91    |
| IV fluid volume (ml), Mean ( $\pm$ SD)             | 1,140.3 (297.9) | 1,000.0 (204.9) | 0.03    |
| Total epinephrine dosage (mg),<br>Mean ( $\pm$ SD) | 4.55 (6.0)      | 0.2 (1.1)       | <0.01   |
| Hypotensive incidence, N (%)                       | 23 (74.2)       | 12 (38.7)       | 0.01    |

**Abbreviations:** Group G = glycopyrrolate group; Group C = control group; SD = standard deviation; mg = milligram; T = thoracic level; EBL = estimated blood loss; ml = millilitre



**Fig 2.** Bar charts with standard error for repeated-measures data.

**Abbreviations:** SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = heart rate; mmHg = millimetre of mercury; beat/min = beats per minute

**TABLE 2.** Statistical analytic results of repeated-measures outcomes.

| Outcome                  | Differences from control | 95% Confidence interval | P-value |
|--------------------------|--------------------------|-------------------------|---------|
| Systolic blood pressure  | 7.4 mmHg higher          | 3.1 to 11.8             | <0.01   |
| Diastolic blood pressure | 4.3 mmHg higher          | 1.7 to 6.9              | <0.01   |
| Mean arterial pressure   | 5.4 mmHg higher          | 2.6 to 8.1              | <0.01   |
| Heart rate               | 1.5 beats/min            | -3.8 to 6.7             | 0.59    |

higher, around 7.4 mmHg (95% CI: 3.1-11.8, p-value<0.01), 4.3 mmHg (95% CI: 1.7-6.9, p-value<0.01), and 5.4 mmHg (95% CI: 2.6-8.1, p-value<0.01), respectively. The graph also shows that the values were maintained for at least the entire 60-minute observation period. Heart rate, however, was no different between the two groups (p-value=0.59).

## DISCUSSION

Spinal anaesthesia is the technique of choice for TURP. It is often preferred over general anaesthesia due to more hemodynamic stability during induction,<sup>19</sup> a lower post-operative analgesic requirement<sup>20</sup>, and less blood loss.<sup>21</sup> This procedure also offers physicians the ability to monitor patient consciousness, which can indicate early

signs of TURP syndrome. These warning signs (such as dizziness, headache, and nausea)<sup>22</sup>, if unaddressed, can lead to cyanosis, hypotension, or even cardiac arrest. TURP patients are also particularly vulnerable to volume overload, as most of them are elderly and have cardiopulmonary disorders. Excessive absorption of irrigation solution through open prostatic venous sinuses during the surgical procedure<sup>10</sup> is the unique cause of this condition. These pose a challenge to the procedure, especially with regard to hemodynamic parameters.

Glycopyrrolate, administered as glycopyrronium bromide, is an anticholinergic drug. It does not cross the blood-brain barrier,<sup>23</sup> has no central nervous system effect, and has fewer chronotropic properties compared to atropine.<sup>12</sup> In anaesthetic practice, glycopyrrolate is commonly used to reverse non-depolarizing muscle relaxants<sup>17,24</sup> or to reduce oral secretions.<sup>25</sup> Some studies have evaluated the effect of glycopyrrolate on hypotension following spinal anaesthesia induction during caesarean delivery.<sup>26-28</sup> According to the pharmacodynamics of glycopyrrolate, it will take effect at about 16.1 minutes and will be cleared about 75.4 minutes after injection. Thus, we decided to apply the drug 15 minutes before performing the procedure. The intramuscular application was chosen to avoid acute tachycardia from the drug's chronotropic effect.<sup>12</sup> Dosage was adjusted to be 0.2 mg to prevent hypertension.<sup>29</sup>

In Thailand, the incidence of spinal anaesthesia-associated hypotension was around 52.6% to 57.9%.<sup>30,31</sup> At age > 65 years, underlying hypertension and use of high doses of bupivacaine were risk factors for TURP patients.<sup>32</sup> Our patients were one of the high-risk groups. With our results, the drug could significantly suppress hypotension. The IV fluid requirement and vasopressor usage were even more reduced, which are attractive for this group of patients, who were vulnerable to fluid overload. Nevertheless, heart rate parameters were not different between the two groups in our study. This finding was partly compatible with the finding from a meta-analysis of glycopyrrolate use in caesarean delivery, that although the drug could maintain a higher heart rate, bradycardia incidence was not different statistically.<sup>26</sup>

There were, however, limitations in our study. Patients with cardiovascular disease and ASA status of more than three were excluded. Further studies are required to evaluate the effectiveness and safety of the drug in patients high ASA status, especially those with cardiovascular disease.

## CONCLUSION

In summary, intramuscular glycopyrrolate may be able to prevent hypotension while decreasing vasopressor and IV fluid usage in elderly spinal anaesthesia TURP patients. Heart rate, however, was not affected.

**Disclosure:** The authors declare that they have no competing interests in this work.

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