

# A Comparison of the Combination of Atropine and Glycopyrrolate with Atropine Alone for the Reversal of Muscle Relaxant

Wichai Ittichaikulthol MD\*, Chawika Pisitsak MD\*,  
Nichawan Wirachpisit MD\*, Paweena Piathong BSN\*,  
Rungphetch Suyawet BSN\*, Rojnarin Komonhirun MEd\*

\* Department of Anesthesiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

**Background:** Muscle relaxant is commonly used in general anesthesia to facilitate surgery. When finishing the operation, anesthesiologists reverse the muscle relaxant with anticholinesterase, neostigmine, combined with anticholinergic for prevention of unwanted side effects from neostigmine. The only existed anticholinergic in Thailand is atropine, which has a more rapid onset than neostigmine resulting in initial tachycardia. Lately, we have glycopyrrolate that cause less increase in initial heart rate. Therefore, we would like to study the effect of heart rate of the combination between atropine and glycopyrrolate to counteract the effect of neostigmine.

**Objective:** Evaluate the different increase in heart rate after the reversal of muscle relaxant with neostigmine combined with atropine or glycopyrrolate plus atropine.

**Material and Method:** The study was a randomized controlled trial study. Fifty-one, ASA I or II patients undergoing elective gynecological surgery under general anesthesia technique were enrolled in the present study. They were randomly assigned by computer-generated random sequence into two groups, control group and intervention group. Control group received neostigmine 2.5 mg and atropine 1.2 mg, intervention group received neostigmine 2.5 mg, glycopyrrolate 0.2 mg and atropine 0.6 mg for reversal of neuromuscular block after finishing the operation. Both groups received the same anesthetic agents including muscle relaxant. Heart rate was recorded before drugs administration and at 1, 3, 5, and 7 minutes after injection. We also recorded heart rate in the PACU at 0, 15, 30, 45, and 60 minutes. Secondary outcome was incidence of arrhythmia during the observation in PACU.

**Results:** There was no difference in age and baseline heart rate between the two groups. There was no different increase in heart rate after administration of reversal agent between control group and intervention group at any time ( $p$ -value = 0.496). No incidence of significant arrhythmia in both groups.

**Conclusion:** There is no significant different increase in heart rate in 0.2 mg glycopyrrolate plus 0.6 mg atropine group compared to 1.2 mg atropine alone for antagonizing muscarinic effects of 2.5 mg neostigmine. Therefore, atropine 0.6 mg and glycopyrrolate 0.2 mg is an alternative to antagonize muscarinic effects of neostigmine.

**Keywords:** Glycopyrrolate, Heart rate, Atropine

*J Med Assoc Thai* 2014; 97 (7): 705-9

**Full text. e-Journal:** <http://www.jmatonline.com>

Muscle relaxant is commonly used in general anesthesia to facilitate the endotracheal intubation and surgical relaxation. After finishing the operation, anesthesiologists reverse the muscle relaxant with anticholinesterase. In Thailand, the authors currently have one type of anticholinesterase, neostigmine. Neostigmine is a quaternary ammonium compound that inhibits acetylcholine esterase at all cholinergic

synapses in the peripheral nervous system. Thus, neostigmine has potent parasympathomimetic activity, which is attenuated or abolished by the administration of an anticholinergic agent, atropine, or glycopyrrolate. Neostigmine effects many organ systems such as cardiovascular system resulting in bradycardia, increase salivation, increase bowel motility, and increase airway resistance. These effects could be prevented and reduced by anticholinergic agents<sup>(1)</sup>. In Thailand, the only anticholinergic agent we have used for many decades is atropine, which is a tertiary amine and easily penetrates the blood-brain barrier and placenta. The intravenous dose of neostigmine and atropine that the authors routinely use are 0.05 mg/kg

**Correspondence to:**

Pisitsak C, Department of Anesthesiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Phone: 0-2201-1513

E-mail: [chawika\\_p@hotmail.com](mailto:chawika_p@hotmail.com)

and 0.02 mg/kg respectively. Many former studies found that the use of neostigmine combined with atropine contribute to more initial tachycardia than neostigmine combined with glycopyrrolate<sup>(2-4)</sup>.

It is more appropriate using glycopyrrolate instead of atropine combined with neostigmine to reverse muscle relaxant effect according to their compatible onset and duration of action. The authors hypothesized that it will cause less increase in initial heart rate and incidence of bradycardia at the recovery room. However, as it is the new medication in Thailand, we still concern about the different reaction of the dosage and its pharmacodynamics for our population. Because the cost of glycopyrrolate is more than atropine, we thought that it would be cheaper to use half-dose of the medication. Thus, the authors decided to use half-dose of glycopyrrolate combined with atropine to counteract the effect of neostigmine.

### Material and Method

After approved by the Institution's Ethics Committee, the present study was conducted at Ramathibodi Hospital. The study was a randomized controlled trial. The inclusion criteria were the ASA I or II patients undergoing elective gynecological surgery between August and December 2013. The exclusion criteria were patients who received beta-blockers, anti-arrhythmic agents, patients with underlying arrhythmia or contraindication to atropine, glycopyrrolate, and neostigmine such as anaphylaxis, including narrow angle glaucoma.

The details of the research were explained to the patients and the informed consents were signed before the randomization. They were randomized into two groups, the intervention group and the control group. All patients were premedicated with 7.5 mg midazolam in the morning of the surgery. When the patients arrived at the operating room, we monitored according to the standard ASA monitoring. After the sign in process was completed, the patients were induced by general anesthesia with endotracheal tube. The anesthetic agents were thiopental, 3-5 mg/kg 0.6 mg/kg atracurium, 0.1 to 0.2 mg/kg morphine, 50% nitrous oxide and oxygen and titration of sevoflurane between 1 and 2%. The intravenous fluid was started with isotonic crystalloid to maintain normal patient hemodynamics and urine output of at least 0.5 ml/kg/hr. Colloids and blood transfusion were administered if there were any indications. At the end of the operation, the patients were administered the reversal agents according to the randomization.

The patients in control group were received 2.5 mg neostigmine and 1.2 mg atropine, the patients in the intervention group were received 2.5 mg neostigmine, atropine 0.6 mg and glycopyrrolate 0.2 mg. The heart rate was recorded before the injection of the reversal agents and at 1, 3, 5, and 7 minutes thereafter. When the patients arrived at the recovery room, we recorded the heart rate at 0, 15, 30, 45, and 60 minutes. Pain was also evaluated by numerical rating scale. If the patients had pain scores more than 4, the pain treatment would be provided by the recovery room staff's order. EKG monitor to detect arrhythmia was also done in both groups.

### Statistical analysis

The authors used mean  $\pm$  SD for continuous data (age, body weight, heart rate and operative time) as well as median, min and max for non-normally distributed data like blood loss (determined by Shapiro-Wilk test). Independent T-test or Mann-Whitney U test, where appropriate, was used to compare numerical data (age, body weight, heart rate, operative time and blood loss) and repeated measures ANOVA was used to compare interval data between groups. The *p*-value  $<0.05$  was accepted as statistically significant.

The sample size of 25 and 26 patients per group were sufficient to achieve 80% power to detect a difference of heart rate of 19 bpm between the control and intervention group according to a previous study<sup>(5)</sup> with a significant level of 0.05 and a number added to prevent unexpected loss of data during the study.

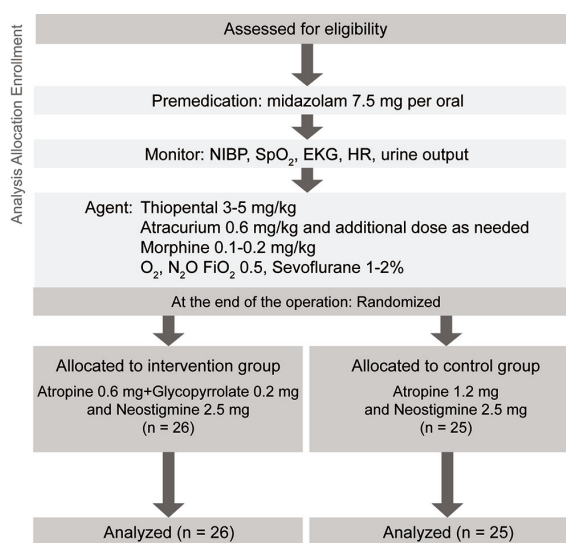


Fig. 1 Flow diagram of the study.

**Table 1.** Baseline characteristics between two groups

	Control group (atropine) (n = 26)	Intervention group (atropine+glycopyrrolate) (n = 25)	p-value
Age (years)	43.12±10.35	47.00±10.53	0.190
Body weight (kg)	62.67±10.11	55.65±7.21	0.006*
Heart rate (bpm)	71.46±9.87	68.80±7.72	0.290
Blood loss (mL), median (max-min)	250 (1,200-50)	400 (2,200-50)	0.538
Operative time (min)	142.31±40.48	165.60±46.47	0.062

Data are mean ± SD unless otherwise stated

\* p-value <0.05

## Results

Fifty-one patients were enrolled in the present study. The patients' baseline characteristics of age and heart rate were similar between groups except the body weight (Table 1). There was no different increase in heart rate after administration of reversal agent between the two groups at any time (p-value = 0.496) (Fig. 2). No incidence of significant arrhythmia occurred in both groups.

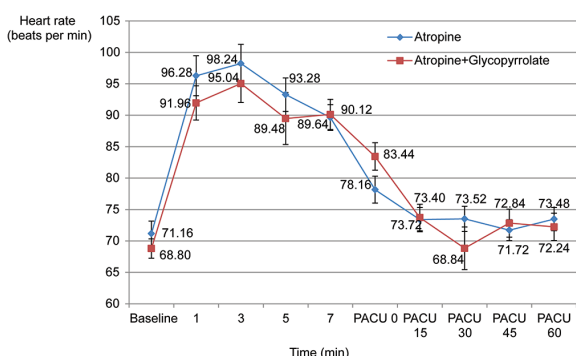
## Discussion

The present study found that there was no significant different of the increase in heart rate in glycopyrrolate plus atropine group compared to atropine alone for antagonizing muscarinic effects of neostigmine. This finding was not consistent with many previous studies.

The authors used half-dose of atropine with small dose of glycopyrrolate for the purpose of avoiding initial tachycardia of high dose atropine, and prevent the incidence of bradycardia from the lower dose of atropine especially in the later

phase, and reduce the cost of the anesthesia on using glycopyrrolate alone. However, we could not demonstrate the benefits except for the cost of anesthesia.

The dosage of the medicine might be an important issue. Salem et al<sup>(3)</sup> conducted a double blinded, randomized, controlled study and found that the only patient who did not show any statistically significant change in heart rate in the immediate post reversal period were those receiving 0.9 mg glycopyrrolate compared with 1.2 mg atropine. If we compared the dose of glycopyrrolate in that study with 0.2 mg glycopyrrolate and 0.6 mg atropine in the present study, it could explain the failing of the initial stability of heart rate in the intervention group due to the much lesser dose of glycopyrrolate. Tribuddharat et al<sup>(5)</sup> did the double blinded, randomized, controlled study on 46 patients to compare 0.9 mg with 1.2 mg atropine to counteract the cholinergic effects of 2.5 mg neostigmine and found that 0.9 mg atropine could prevent cholinergic effect and cause lesser increase in heart rate. Wetterslev et al<sup>(6)</sup> conducted a randomized controlled trial to compare the effects of the heart rate of a single dose 7 mcg/kg glycopyrrolate and two doses of 8 mcg/kg atropine at an interval of 10 minutes. There was no significant difference in heart rate and the cholinergic effects between groups. If we use this dose in our population, the dose of atropine will equal to two doses of 0.4 mg. This research also supports the hypothesis of lesser dose of atropine, which will cause less initial tachycardia. These evidences influence our research to use 0.6 mg atropine in the intervention group. In the present study, the authors decide to use 0.6 mg atropine but the authors still could not demonstrate the difference of the initial increase in heart rate between groups. The discrepancy of the result from other studies might come from the various techniques of the general anesthesia including the



**Fig. 2** Comparison of heart rate between two groups\*.  
\* Comparison of heart rate between two study groups performed by repeated measures ANOVA (p-value = 0.496).

choice of anesthetic agents among the hospitals. The definite result should come from the controlled trial that use the same technique and possibly in the same center.

There were also some limitations in the present study. First, we could not blind the observer in the operating room, because it is the organization practice that anesthesiologists need to identify the drug given to the anesthetized patients. Second, we did not control the anesthetic management that could affect the result, especially the cardiovascular response at the end of the operation such as the onset and duration of the suction, the depth of the anesthesia before the extubation.

The authors selected the patients with ASA physical status I-II. Thus, the present study cannot apply to the older and high-risk groups that might have benefit from the lesser dose of atropine<sup>(4,7,8)</sup>. Further studies are required to prove the benefits of the combination of atropine and glycopyrrolate to reverse the cholinergic effects of neostigmine by adjusting dose and patient selection.

In conclusion, there is no significant different increase in heart rate in glycopyrrolate plus atropine group compared to atropine alone for antagonizing muscarinic effects of neostigmine. Therefore, atropine 0.6 mg and glycopyrrolate 0.2 mg is an alternative to antagonize muscarinic effects of neostigmine.

#### **What is already known on this topic?**

Anticholinesterase agent, which is used to reverse muscle relaxant, has several side effects. Anticholinergic can counteract these unwanted effects. There is varied combination of these two drugs but neostigmine and atropine are the only combination in Thailand. However, the matching onset and duration of them are problematic because atropine has more rapid onset and shorter duration of action compared with neostigmine. Therefore, the initial tachycardia in the patients who receive these combination agents are quite common. Although, there is lack of evidence about the increasing mortality of this practice but there is better combination agents available overseas. The suitable agent that is appropriate to combine with neostigmine is glycopyrrolate.

#### **What this study adds?**

Currently, the authors have glycopyrrolate available in Thailand. The evidence of the better outcomes especially the initial increase in heart rate when using full dose of atropine instead of

glycopyrrolate to counteract the muscarinic effect of neostigmine is well known.

Therefore, the present study was designed to use half dose of glycopyrrolate and atropine to antagonize the effect of neostigmine compared with atropine alone. In Thailand, the cost of glycopyrrolate is higher than atropine. The background of the half dose of both atropine and glycopyrrolate came from the objective to reduce cost together with the elimination of the risk of initial bradycardia from single, small dose of glycopyrrolate.

The authors found that half dose of glycopyrrolate plus atropine has no significant difference in initial heart rate compared with atropine alone for antagonizing muscarinic effects of neostigmine. If the authors still want to use glycopyrrolate combined with atropine to antagonize neostigmine, the authors need to adjust dose of both drugs in the future study.

#### **Potential conflict of interest**

None.

#### **References**

1. Fassi A, Rosenberg M. Atrophine, scopolamine, and glycopyrrolate. *Anesth Prog* 1979; 26: 155-9.
2. Ostheimer GW. A comparison of glycopyrrolate and atropine during reversal of nondepolarizing neuromuscular block with neostigmine. *Anesth Analg* 1977; 56: 182-6.
3. Salem MG, Ahearn RS. Atropine or glycopyrrolate with neostigmine 5 mg: a comparative dose-response study. *J R Soc Med* 1986; 79: 19-21.
4. Dworacek B, Ruprecht J, Bode A, Walhout MJ. Atropine methylbromide and glycopyrrolate. A comparative study during reversal of neuromuscular block. *Acta Anaesthesiol Belg* 1987; 38: 147-52.
5. Tribuddharat S, Sathitkarnmanee T, Naewthong P. Less tachycardia in adults when using atropine 0.9 mg compared with 1.2 mg plus neostigmine 2.5 mg. *J Med Assoc Thai* 2008; 91: 665-8.
6. Wetterslev J, Jarnvig I, Jorgensen LN, Olsen NV. Split-dose atropine versus glycopyrrolate with neostigmine for reversal of gallamine-induced neuromuscular blockade. *Acta Anaesthesiol Scand* 1991; 35: 398-401.
7. Mirakhur RK. Antagonism of neuromuscular block in the elderly. A comparison of atropine and glycopyrrolate in a mixture with neostigmine. *Anaesthesia* 1985; 40: 254-8.

8. Mostafa SM, Vucevic M. Comparison of atropine and glycopyrronium in patients with pre-existing cardiac disease. *Anaesthesia* 1984; 39: 1207-13.

---

การศึกษาเปรียบเทียบการใช้ *atropine* ร่วมกับ *glycopyrrolate* กับ *atropine* เพียงอย่างเดียว ในการแก้ฤทธิ์ยาหย่อนกล้ามเนื้อในระหว่างผ่าตัด

วิชัย อธิธิชัยกุลทล, ชวิกา พิสิฐฐศักดิ์, ณิชาวรรณ วิรัชพิสิฐ, ปวีณา เปียทอง, รุ่งเพชร สุขะเวช, โรจนรินทร์ โกมลหิรัญ

ภูมิหลัง: ยาหย่อนกล้ามเนื้อได้นำมาใช้เป็นส่วนหนึ่งของการให้ยาระงับความรู้สึกแบบทั่วไป เมื่อเสร็จสิ้นการผ่าตัดวิสัญญีแพทย์จะแก้ฤทธิ์ยาหย่อนกล้ามเนื้อด้วย *neostigmine* ซึ่งเป็นยากดเอนไซม์ *anticholinesterase* ร่วมกับยา *anticholinergic* เพื่อป้องกันผลอันไม่พึงประสงค์ของยา *neostigmine* ในประเทศไทยใช้ยา *atropine* แก้ฤทธิ์ *neostigmine* มานานแล้ว แต่มีข้อเสียทำให้หัวใจเต้นเร็วในระยะต้น ปัจจุบันเริ่มมีการนำ *glycopyrrolate* เข้ามาในประเทศไทย ซึ่งมีหลักฐานทำให้เกิดหัวใจเต้นเร็วในระยะต้นน้อยกว่า ผู้นิพนธ์จึงมีความสนใจศึกษาเปรียบเทียบผลของยา *glycopyrrolate* ร่วมกับยา *atropine* ในการแก้ฤทธิ์ *neostigmine*

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบผลต่างของอัตราการเต้นของหัวใจ จากการให้ยา *glycopyrrolate* 0.2 มก. ร่วมกับ *atropine* 0.6 มก. เปรียบเทียบกับ *atropine* 1.2 มก. เพื่อลดผลข้างเคียงของยา *neostigmine* 2.5 มก. ในการต้านฤทธิ์ยาหย่อนกล้ามเนื้อ

วัสดุและวิธีการ: ทำการศึกษาแบบสุ่มไปข้างหน้าและมีกลุ่มควบคุม มีผู้เข้าร่วมการศึกษา 51 ราย เป็นผู้ป่วย ASA I-II ที่มารับการผ่าตัดทางนรีเวช โดยวิธีการระงับความรู้สึกแบบทั่วไป ถูกสุ่มแบ่งเป็นสองกลุ่มด้วยคอมพิวเตอร์ ได้แก่ กลุ่มควบคุมและกลุ่มทดลอง ทั้งสองกลุ่มได้รับยาระงับความรู้สึกและยาหย่อนกล้ามเนื้อที่เหมือนกัน เมื่อเสร็จการผ่าตัด กลุ่มควบคุมได้รับยา *atropine* 1.2 มก. และ *neostigmine* 2.5 มก. กลุ่มทดลองได้รับยา *glycopyrrolate* 0.2 มก., *atropine* 0.6 มก. และ *neostigmine* 2.5 มก. มีการจดบันทึกอัตราการเต้นของหัวใจก่อนฉีดยาและหลังฉีดยา ที่เวลา 1, 3, 5, 7 นาที และบันทึกอัตราการเต้นของหัวใจ ขณะอยู่ในห้องพักฟื้นที่เวลา 0, 15, 30, 45, 60 นาที ร่วมกับคะแนนปวดและการเกิดหัวใจเต้นผิดจังหวะอื่น ๆ

ผลการศึกษา: ผู้เข้าร่วมการศึกษาทั้งสองกลุ่มไม่มีความแตกต่างอย่างมีนัยสำคัญ ในอายุ อัตราการเต้นของหัวใจก่อนให้ยา ไม่พบการเปลี่ยนแปลงอัตราการเต้นของหัวใจหลังได้รับยาในทุกช่วงเวลาอย่างมีนัยสำคัญทางสถิติ ( $p = 0.496$ ) และไม่พบการเกิดภาวะหัวใจเต้นผิดจังหวะ

สรุป: การเปลี่ยนแปลงของอัตราการเต้นของหัวใจ หลังการแก้ฤทธิ์ยาหย่อนกล้ามเนื้อด้วย *neostigmine* 2.5 มก. ร่วมกับ *atropine* 1.2 มก. ไม่มีความแตกต่างกับ *neostigmine* 2.5 มก. กับ *atropine* 0.6 มก. และ *glycopyrrolate* 0.2 มก. อย่างมีนัยสำคัญทางสถิติ ดังนั้น *atropine* 0.6 มก. ร่วมกับ *glycopyrrolate* 0.2 มก. จึงเป็นอีกทางเลือกหนึ่งในการแก้การข้างเคียงของ *neostigmine*

---