Less Tachycardia in Adults when Using Atropine 0.9 mg Compared with 1.2 mg Plus Neostigmine 2.5 mg

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Objective: *Compare the increase in heart rate in adults after 0.9 vs. 1.2 mg of atropine plus neostigmine 2.5 mg as the non-depolarizing muscle relaxant reversal agent.*
Material and Method: *A randomized, double blind, controlled trial on 46 adults ASA I-II, undergoing elective gynecological or general surgery with balanced general anesthesia was performed. The subjects were randomized into two groups, After surgery, the study group received 0.9 mg of atropine, while the control group received 1.2 mg of atropine. Both groups received 2.5 mg of neostigmine simultaneously.*
Results: *The heart rate and blood pressure were taken at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, and 30 min after the injection. The increase in heart rate and blood pressure between the two groups were compared. The heart rate (at 3, 4, 5, and 6 min) of patients in the study group increased significantly less than that of patients in the control group. There was no significant difference in blood pressure between groups and no side effects occurred.*
Conclusion: *The authors conclude that 0.9 mg of atropine with 2.5 mg neostigmine can be safely used as the reversal agent for a non-depolarizing muscle relaxant, particularly in patients for whom any increase in heart rate would be harmful.*

Keywords: *Agent, Atropine, Increase in Heart Rate, Reversal*

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Atropine plus neostigmine have been used as the reversal agent for the non-depolarizing muscle relaxant vecuronium at the end of general balanced anesthesia, but the standard dose of 1.2 mg usually causes tachycardia[1,2], which may pose a serious risk to patients with coronary artery disease (CAD)[3], thyrotoxicosis, or hypovolemia[4-6]. The authors compared the increase of heart rate, blood pressure, and side effects caused by 0.9 vs. 1.2 mg of atropine with an aim to reduce the dose to 0.9 mg.

The primary outcomes for comparing 0.9 vs. 1.2 mg of atropine were the increase of heart rate, blood pressure, and side effects. It was estimated that a sample size of 23 subjects per group would provide approximately 80% power for assessing equivalence in a two tailed test ($\alpha = 0.05$) to detect 30% less increase in heart rate in the study group. The descriptive data were presented as means $\pm$ SD. The Mann-Whitney U test was used to compare the increase in heart rate and blood pressure from the baseline of the two groups ($p < 0.05$).

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Material and Method

The design of the present study was a randomized, double blind, controlled trial (using a block-of-four randomization put in opaque envelops). Written informed consent was sought. The present study included adult patients, 15 years of age and over, ASA I-II, scheduled to undergo elective gynecological or general surgery with standard general anesthesia with endotracheal intubation and controlled ventilation. The authors excluded patients with hypovolemia, those receiving drugs affecting the heart rate (*i.e.* α or β -blocker, digitalis, calcium channel blocker and ACE inhibitor) and patients with arrhythmia or tachycardia,

such as thyrotoxicosis and heart disease. The present study was reviewed and approved by the Ethics Committee of Khon Kaen University.

The anesthesia was induced with sodium thiopentone (3-5 mg/kg) and intubation facilitated with succinylcholine (1-1.5 mg/kg). Maintenance was accomplished with nitrous oxide (66%), isoflurane (0.6-1.2%), fentanyl (1 μg/kg) plus vecuronium (0.1 mg/kg) as the non-depolarizing muscle relaxant.

At the end of surgery, the 46 patients were randomized into two groups: 1) the study group who received 0.9 mg atropine plus 2.5 mg of neostigmine; and 2) the control group who received 1.2 mg of atropine plus 2.5 mg of neostigmine. Both drug combinations were prepared by an anesthesiologist outside the operating theater to have equal volume of 3 ml by adding 0.5 ml of sterile water to the study drug. The drugs were injected simultaneously. The anesthesiologist who injected the drugs and the assessor were all blinded.

Heart rate, blood pressure, and side effects were measured and recorded at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, and 30 min after injecting the reversal drug.

Statistical analysis

All of the descriptive data were presented as means ± SD. The Mann-Whitney U test was used to compare any increase in heart rate and blood pressure vis-□-vis the baseline of the two groups. A p-value of < 0.05 was considered significant.

Results

There were 23 patients in each group and the demographics between groups were similar excepted heart rate (Table 1). The heart rate of the control group was slightly higher than the study group at the beginning of the present study (81.61 vs. 74.43 bpm), but the primary outcome was the increase of the heart rate from 0 min after injecting the drugs. The increase in heart rate in the study group was significantly less than the control group at 3, 4, 5 and 6 min from the baseline (T_0) (Table 2). The differences in blood pressure between groups were insignificant. No bradycardia, dysrhythmia, or other side effect occurred.

Discussion

The use of 1.2 mg of atropine plus 2.5 mg of neostigmine to reverse the effects of non-depolarizing muscle relaxant in adults usually causes tachycardia[1,2], which may be risky for geriatric patients[3], and patients with CAD, thyrotoxicosis or hypovolemia[4-6]. Several studies compared atropine with glycopyrrolate and concluded that glycopyrrolate caused less increase in heart rate and should be the drug of choice[7-11]. Notwithstanding, glycopyrrolate is not available in Thailand, thus atropine is still used.

Table 1. Baseline demographics characteristics: study vs. control groups

	Atropine 0.9 mg (n = 23) (Study group)	Atropine 1.2 mg (n = 23) (Control group)
Gender (M/F)	4/19	3/20
Age (y)	41.91 ± 10.95	41.78 ± 10.06
Weight (kg)	56.44 ± 11.22	55.20 ± 6.43
Heart rate (bpm)	74.43 ± 11.82	81.61 ± 9.99*
Systolic BP (mmHg)	122.52 ± 12.71	124.30 ± 16.59
Diastolic BP (mmHg)	83.43 ± 10.21	82.22 ± 9.04

* $p < 0.05$

Table 2. Increase in heart rate (bpm) from baseline (T_0): study vs. control groups

Min from T_0	1	2	3	4	5	6	7	8	9	10
Study group	22.9	25.4	19.9	14.2	7.5	3.9	3.4	2.0	-0.6	-1.9
Control group	29.4	31.8	30.9	25.6	20.8	15.3	11.2	9.7	6.7	3.4
p-value	0.116	0.169	0.011	0.019	0.007	0.013	0.060	0.111	0.091	0.026

* $p < 0.05$

Some studies investigated different ways of administering atropine to reduce the side-effects. Wetterslev et al[12] reported that a split-dose of atropine had the same effect as a single dose of glycopyrrolate, but induced frequent cardiac arrhythmias. Harper et al[13] found that a slow-injection over 3 minutes lessened and delayed the initial rise in heart rate.

Some researchers tried reducing the dose of atropine. For example, d'Hollander et al[14] used 0.75 mg of atropine but significant bradycardia occurred. Two trials used 0.9 mg of atropine but bradycardia occurred albeit without any significant change in blood pressure[15,16].

The authors found that 0.9 mg of atropine caused less increase in heart rate than 1.2 mg at 3,4,5 and 6 min (i.e. the peak potential for tachycardia of both drugs). The significance increases in heart rate were 3.9-19.9 bpm and 15.3-30.9 bpm in the study and control groups, respectively. No bradycardia, dysrhythmia, or other side effect was found in the study group. The difference between our study and the studies of d'Hollander et al[14] and Heinonen et al[15,16] is that the muscle relaxants used in those studies were pancuronium and alcuronium which had more cardiovascular side effects than vecuronium in the present study. Thus, 0.9 mg of atropine is safe and may be considered in patients who tachycardia is unfavorable.

Conclusion

A lower dose of atropine (0.9 mg) with 2.5 mg of neostigmine resulted in a significantly lower increase in heart rate than 1.2 mg of atropine with neostigmine at 3, 4, 5, and 6 min after injection without any side effect. This protocol may be used in patients in whom tachycardia is unfavorable.

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การใช้ atropine 0.9 มก.ทำให้อัตราการเต้นของหัวใจเพิ่มน้อยกว่า atropine 1.2 มก. เมื่อให้ร่วมกับ neostigmine 2.5 มก.ในผู้ใหญ่

สิริรัตน์ ตรีพุทธรัตน์, เทพกร สาธิตการมณี, เพ็ญวิสา แนวทอง

วัตถุประสงค์*: เพื่อศึกษาเปรียบเทียบการเพิ่มของอัตราการเต้นของหัวใจระหว่าง atropine 0.9 มก. และ 1.2 มก. เมื่อให้ร่วมกับ neostigmine 2.5 มก. ในการแก้ฤทธิ์ของยาหย่อนกล้ามเนื้อชนิด non-depolarizing ในผู้ใหญ่*

รูปแบบการวิจัย*: prospective randomized, double blind, controlled trial*

วัสดุและวิธีการ*: ผู้ป่วยผู้ใหญ่ 46 ราย ASA I-II ที่มารับการผ่าตัดทางนรีเวชและศัลยกรรมโดยการระงับความรู้สึกชนิด balanced general anesthesia ถูกสุ่มแยกเป็น 2 กลุ่ม กลุ่มศึกษาได้รับ atropine 0.9 มก. ขณะที่กลุ่มควบคุมได้รับ atropine 1.2 มก.ร่วมกับ neostigmine 2.5 มก.เพื่อแก้ฤทธิ์ยาหย่อนกล้ามเนื้อชนิด non-depolarizing เมื่อเสร็จผ่าตัด บันทึกอัตราการเต้นของหัวใจและความดันเลือดที่นาทีที่ 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 และ 30 หลังได้รับยา เปรียบเทียบการเพิ่มของอัตราการเต้นของหัวใจและความดันเลือดของทั้ง 2 กลุ่มที่แต่ละเวลา*

ผลการศึกษา*: อัตราการเต้นของหัวใจที่นาทีที่ 3, 4, 5 และ 6 ของกลุ่มศึกษาเพิ่มขึ้นน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ ทางสถิติ ส่วนความดันเลือดแตกต่างอย่างไม่มีนัยสำคัญ ไม่พบอาการข้างเคียง*

สรุป*: การใช้ atropine 0.9 มก.ร่วมกับ neostigmine 2.5 มก.เพื่อแก้ฤทธิ์ของยาหย่อนกล้ามเนื้อชนิด non-depolarizing หลังผ่าตัดทำให้อัตราการเต้นของหัวใจเพิ่มน้อยกว่า atropine 1.2 มก. จึงน่าจะใช้ได้โดยปลอดภัยโดยเฉพาะอย่างยิ่งในผู้ป่วยที่อาจมีอันตรายจากภาวะหัวใจเต้นเร็ว*