Original article

The effect of dexmedetomidine on the vagolytic effect of pancuronium during propofol induction

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Objective To determine the effect of dexmedetomidine on the vagolytic effect of pancuronium during propofol induction and the hemodynamic responses to intubation in normotensive patients plus the effects of dexmedetomidine on the action of pancuronium

Methods Forty-four American Society of Anesthesiologists (ASA) class I and II adults were included in this randomized, double-blind controlled trial. Patients with hypertension or preexisting bradycardia/tachycardia were excluded from the study. On arrival at the operating room, participating patients received a 20 ml infusion of either saline (Group C, n=22) or Dexmedetomidine 0.7 μg/kg (Group D, n=22) over a period of 10 minutes followed by propofol induction. Calibration of the twitch response of the adductor pollicis muscle was then performed followed by injection of pancuronium 0.12 mg/kg. Endotracheal intubation was accomplished 2.5 minutes after the injection. Initial blood pressure (BP) and heart rate (HR) were measured and recorded for baseline control. BP and HR were measured again at completion of drug infusion, 2.5 minutes after pancuronium, immediately after intubation, and then each minute for the next 5 minutes for a total of 5 times (T0-T5). Also recorded was the twitch height of the adductor pollicis muscle at the time of intubation and the duration of action of pancuronium.

Results The HR in Group D was lower than that of Group C at 2.5 minutes after pancuronium (75.7±9.3 vs 88±12.9 bpm, p=0.013) but not different from its baseline. After intubation, HR at T0-T5 were comparable between groups. BP did not differ significantly between the groups during the entire study. In Group C, however, systolic BP at just before intubation was significantly lower than baseline (106.4±12.0 vs 121.0±13.9 mmHg, p=0.001). None of the patients needed treatment for hypo/hypertension or brady/tachycardia. At the time of intubation, Group D had a higher percentage of patients with a twitch height <10% than Group C (92 vs 67%, p=0.048). The duration of action of pancuronium was not different between the groups.

Conclusions In normotensive patients, dexmedetomidine 0.7μg/kg infusion prior to propofol induction effectively reduces the vagolytic effect of pancuronium prior to intubation but does not blunt the blood pressure responses to intubation. It also quickens the onset of pancuronium but has no effect on its duration. **Chiang Mai Medical Journal 2017;56(2):81-8.**

Keywords: Dexmedetomidine, pancuronium, vagolytic effect, intubation, hemodynamic

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Introduction

Pancuronium, an aminosteroidal muscle relaxant which was developed in the 1960s, is still widely used in many developing countries (1). This is partly due to its low price and partly to its vagolytic action which leads to more cardiovascular stability during anesthesia, particularly in some high risk groups such as patients with fixed low cardiac output (2-4). However, at the higher dose necessary for intubation, its vagolytic effect is more intense, resulting in greater increases in heart rate and blood pressure. These changes are much greater during intubation and can be harmful to patients with preexisting hypertension.

Dexmedetomidine, a selective α2 agonist with sedative and analgesic effects, has been widely used to decrease hemodynamic responses to intubation (5,6). It decreases blood pressure and heart rate by centrally mediated sympatholytic effects and by decreasing norepinephrine release at neuroeffector junctions (7). Furthermore, it has been reported that in some cases it can affect the muscle relaxant-induced twitch suppression, resulting in a prolonged duration of action of the relaxant (8,9). This study aimed to determine the effect of dexmedetomidine on the vagolytic effect of pancuronium during propofol induction and the hemodynamic responses to intubation in normotensive patients as well as its effects on the action of pancuronium.

Methods

After receiving approval from the ethic committee of the Faculty, and signed informed consent forms were obtained, 44 adult patients (ASA physical status I-II, age 18-60, BMI <30) who were scheduled for elective surgery under general endotracheal anesthesia were included in the study. Patients who had cardiovascular diseases (blood pressure > 140/90 mmHg, ischemic heart disease, heart block, heart rate >100 or <60 beats/min), neuromuscular diseases, or who had received drugs known to interact with muscle relaxant were excluded. Additional exclusion criteria included patients who had hyperthyroidism, renal insufficiency (creatinine clearance <60%), hepatic insufficiency, and cases where difficult intubation was anticipated. Two hours before anesthesia, all the participants were administered oral midazolam 7.5 mg as a premedication drug. After the patients arrived at the operating room, standard monitoring procedures (non-invasive automated blood pressure, electrocardiography, pulse oximetry and capnography) were initiated for all. The patients were then allocated randomly into one of two groups using a computer-generated block of 4 randomization numbers sealed in an opaque envelope. The control group (Group C, n=22) received saline while the dexmedetomidine group (Group D, n=22) received dexmedetomidine infusion (0.7 μg/kg) at the same volume of 20 mL over a period of 10 minutes followed by propofol 2.5 mg/kg. Calibration of the twitch response (single twitch 1 Hz, TOF Watch™) of the adductor pollicis muscle to ulnar nerve stimulation at either wrist was then performed and followed by administration of pancuronium 0.12 mg/kg. Endotracheal intubation was performed 2.5 minutes after the pancuronium by an anesthesiologist who was unaware of the patients' group. Prior to intubation, the patients were manually ventilated with 50% N_2O in O_2 (total flow 6 L/min) followed by 67% N_2O in O_2 at the same flow rate for 5 minutes following intubation. After that, anesthesia was maintained by 1.5% sevoflurane and fentanyl 2 μg/kg, and the ventilation was controlled to keep the end-tidal CO_2 at 35-40 mmHg. At the same time, the mode of ulnar nerve stimulation was changed to a train-of-four (TOF). The investigation ended when the second TOF count resumed.

Blood pressure, including systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), as well as heart rate (HR) were measured and recorded at baseline, upon completion of drug infusion, 2.5 minutes after pancuronium, immediately after intubation (T0), and each minute after that for five minutes, a total of five times (T1-T5). Also recorded were the twitch height (% of control) of the adductor pollicis muscle at the time of intubation, intubation time (seconds), and the duration of action of pancuronium (the time from injection of pancuronium to TOF count back to 2, min). All data were recorded by a member of the investigation team who was blinded to the patient groups.

Incidents of severe hypotension and bradycardia were also recorded. Had that situation occurred, after rescue treatment with intravenous ephedrine or atropine was administered, the investigation of that patient would have been terminated. During the study, all patients were kept warm so that the temperature of skin over the thenar muscle remained at > 32 ^{o}C.

Continuous data are presented as mean (SD), whereas categorical data are given as n and percent. Statistical analysis was performed using paired and unpaired Student's t-test or Fisher's exact test as appropriate. P values of less than 0.05 were considered statistically significant.

Results

Patient demographic data were comparable between the groups, including intubation time and the temperature of skin over the thenar muscle (Table 1). Hemodynamic responses are shown in Figures 1 (HR), 2 (SBP), 3 (DBP), and 4 (MAP). The HR in Group D was lower than that of Group C at 2.5 minutes after pancuronium (75.7±9.3 vs 88±12.9 bpm, *p*= 0.013), but not different from its baseline. After intubation, HR from T0 to T5 were comparable between groups. Regarding BP, all SBP, DBP and MAP were not significantly different between groups during the entire study. In Group C, however, the SBP before intubation was significantly lower than the group baseline (106.4±12.0 vs 121.0±13.9 mmHg, *p*=0.001). No patients needed treatment due to hypo/hypertension or brady/tachycardia. At the time of intubation, Group D had a higher percentage of patients with a twitch height of <10% than Group C (92 vs 67%, *p*=0.048). The duration of pancuronium were not different between groups (95.9±26.3 and 96.2±22.5 min in Group D and Group C respectively).

Discussions

Dexmedetomidine, a selective α2 agonist, decreases blood pressure and heart rate through centrally mediated sympatholytic effects and by decreasing norepinephrine release at neuroeffector junctions. In addition, it has an indirect effect on the ventrolateral preoptic nucleus in the anterior hypothalamus and its descending pathway in controlling the natural sleep pathway. This is one of the main mechanisms of dexmedetomidine-induced sedation (10) which results in a reduction in anesthetic requirements (5,6,11-13). Both laryngoscopy and intubation can stimulate significant hemodynamic responses as well as an increase in catecholamines which can result in tachycardia, hypertension and increased myocardial O_2 demand. These hemodynamic responses are usually transient, however, they can last longer and have greater intensity in hypertensive patients which can lead to morbidity. Dexmedetomidine has been used safely as an anesthetic adjuvant in patients undergoing high risk surgery (13-15). Tanskanen et al.(15) demonstrated that when dexmedetomidine was used as an anesthetic adjuvant in patients undergoing intracranial tumor surgery, it could minimize the increase in heart rate after pancuronium 0.1 mg/kg (5 vs 22 beats/min in the control group). In the present study, it was concluded that dexmedetomidine 0.7 μg/kg infusion effectively reduced the degree of tachycardia caused by the vagolytic effect of pancuronium prior to intubation but not after intubation, nor could it blunt the pressure responses to intubation. Dexmedetomi-

Table 1. Patient characteristics

Variables	Group D (n=22)	Group C (n=22)	*P-value*
Age (yr) mean±SD	36.1±13.7	36.8±14.2	0.872
Gender=n (%)			0.128
Female	15 (68.2%)	10 (45.5%)	
Male	7 (31.8%)	12 (54.5%)	
Height (cm) mean±SD	159.4±6.6	160.2±10.0	0.778
Weight (kg) mean±SD	54.2±8.1	56.4±8.3	0.374
BMI mean ± SD	21.3±2.9	22.0±2.4	0.394
ASA physical status classification=n (%)			0.472
ASA I	16 (72.7%)	18 (81.8%)	
ASA II	6 (27.3%)	4 (18.2%)	
Skin temperature at start (°C) mean±SD	34.2±1.4	33.9±1.2	0.582
Skin temperature at finish (°C) mean±SD	34.5±0.8	34.2±0.9	0.380
Intubation time (sec) mean±SD	13.5+8.0	14.1+9.0	0.819

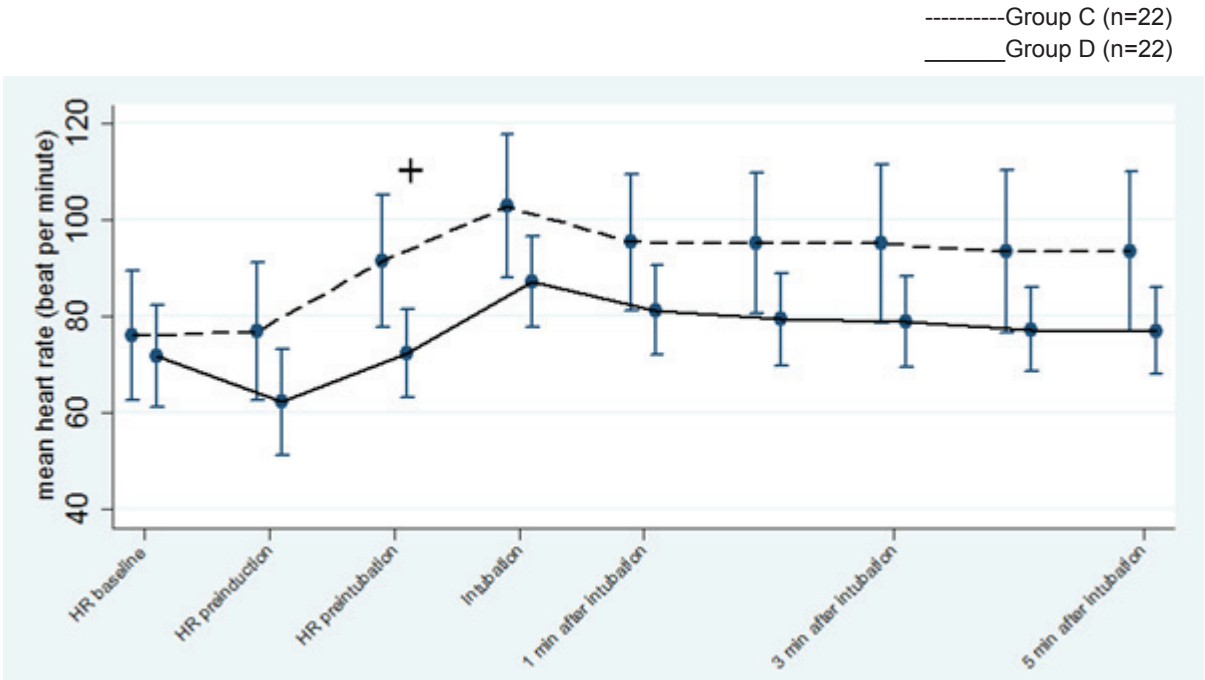

Figure 1. Comparison of heart rate (HR). + At preintubation (2.5 min after pancuronium), Group C (control) had a significantly higher HR than Group D (dexmedetomidine) (p=0.013).

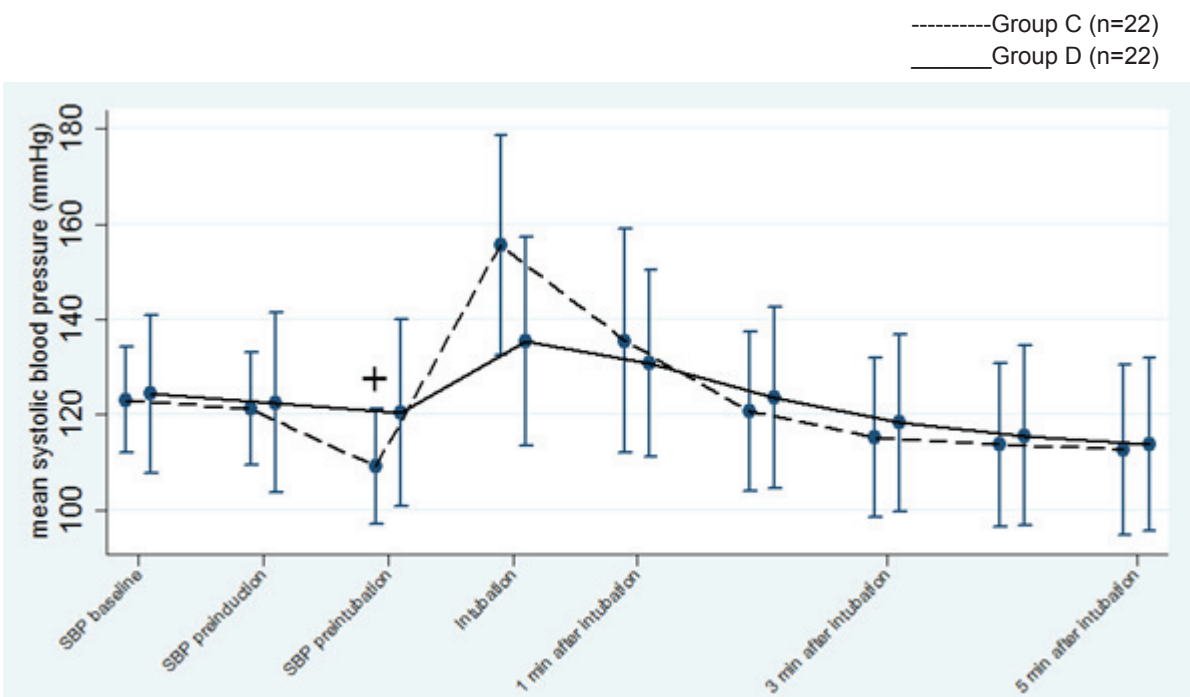

Figure 2. Comparison of systolic blood pressure (SBP). SBP was comparable between groups. In group C (control), + the SBP at preintubation (2.5 min after pancuronium) was significantly lower than its baseline values (p=0.001).

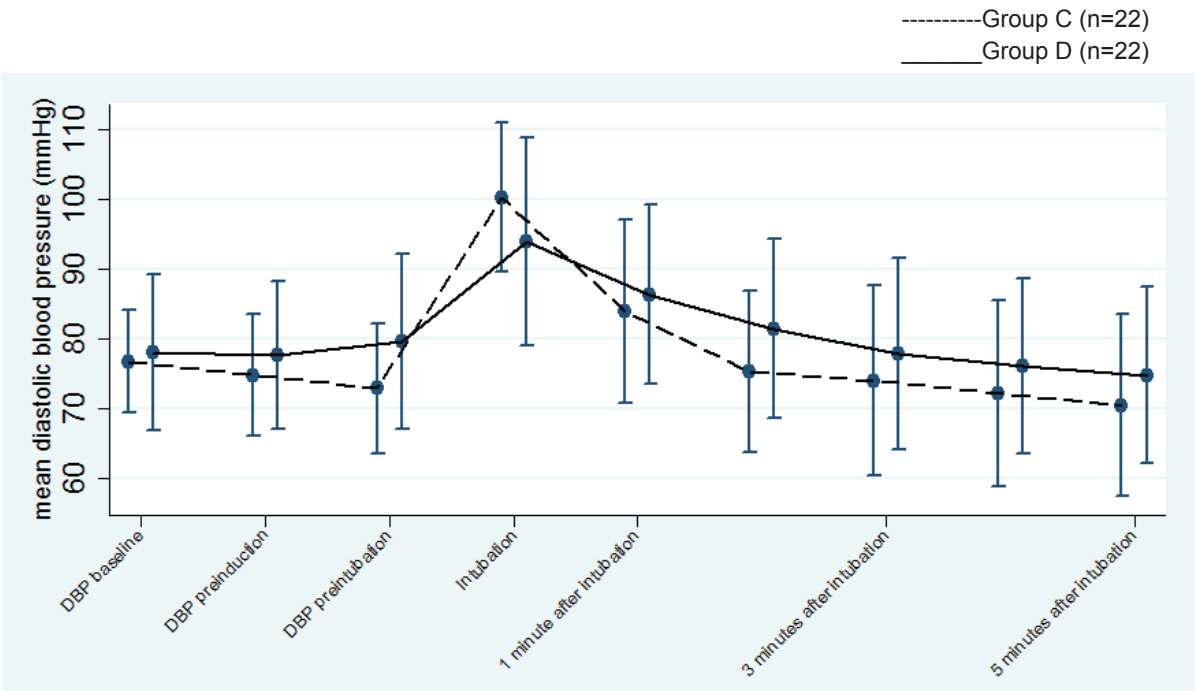

Figure 3. Comparison of diastolic blood pressure (DBP). DBP were comparable between groups.

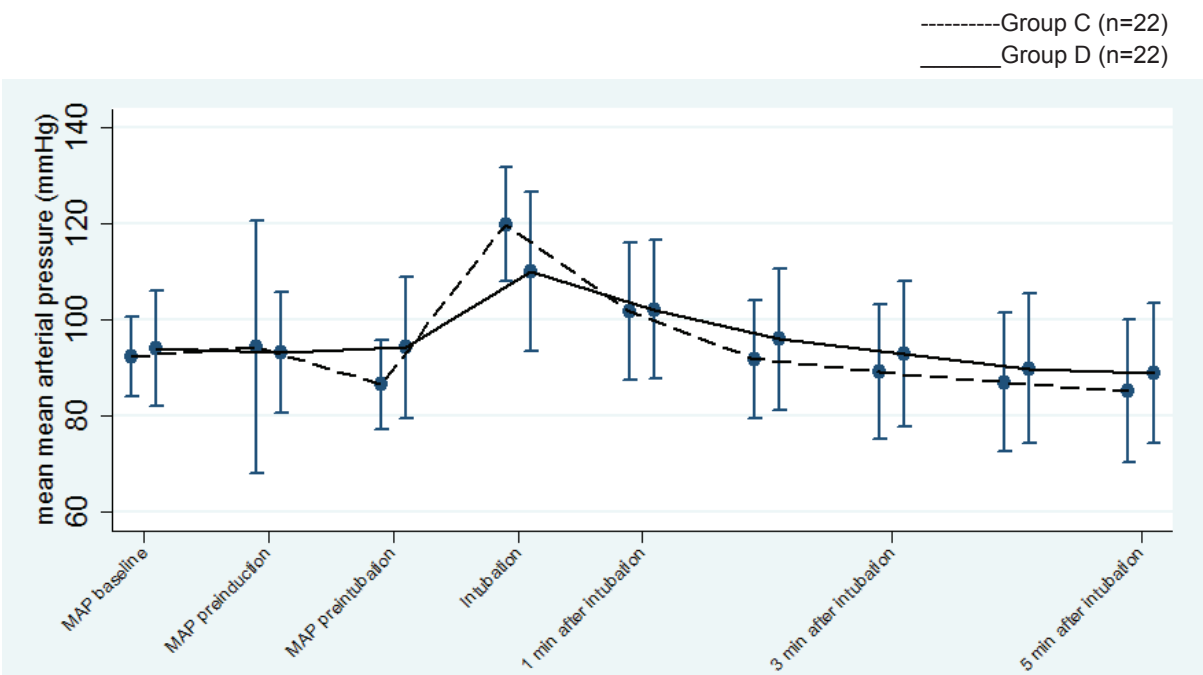

Figure 4. Comparison of mean arterial pressure (MAP). MAP was comparable between groups.

dine itself can also increase blood pressure due to its effect being mediated by agonism at the peripheral α2 receptor of vascular smooth muscle, but only when administered rapidly and at a high dose. In our previous study (16), dexmedetomidine 0.7 μg/kg infusion was found to effectively attenuate the hemodynamic responses to double-lumen endotracheal intubation but only in conjunction with 1% sevoflurane. In order to blunt the hemodynamic responses, a higher dose of dexmedetomidine and/or other adjuvant drugs should be considered because greater responses can be anticipated due to the combined effects of intubation and pancuronium.

The neuromuscular blocking property of dexmedetomidine is unlikely to be its action at the neuromuscular junction. Rather, a high dose dexmedetomidine would affect the twitch response via cardiovascular suppression, resulting in subsequent decreases in both renal and hepatic blood flow as well as an increase in plasma concentration of the relaxant (9,13). Though we did not observe a significant blood pressure difference between groups, the systolic blood pressure before intubation in the control group was significantly lower than its baseline control. Dexmedetomidine exhibits peripheral α2 agonism in vascular smooth muscle, though only at high doses, which can result in a more stable BP during propofol induction. Ezri et al (17). concluded that the significant reduction or prolongation of the rocuronium onset time in patients pretreated with ephedrine or esmolol might be due to changes in cardiac output produced by these agents. This might explain why the dexmedetomidine group had a lower average twitch height at intubation, a reflection of a more rapid onset of pancuronium. A single dose of 0.7 μg/kg of dexmedetomidine had no effect on the duration of pancuronium; however, in the case of higher doses or continuous infusion, it would probably affect pancuronium-induced twitch suppression, resulting in a prolonged duration of action.

This study had some limitations. First, we did not measure the plasma levels of catecholamines, dexmedetomidine or pancuronium, so we could not determine the effective dose of dexmedetomidine for decreasing sympathetic activity. In addition, we could not demonstrate whether the change in blood pressure had an effect on the plasma level of pancuronium. Second, cardiac output was not measured. Usually, BP does not correlate well with cardiac output. The drop in BP in the control group prior to intubation might not explain the delayed onset of pancuronium if the CO was maintained at a normal level. Lastly, complete blinding could not be achieved due to the observable effects of dexmedetomidine on HR and sedation level.

Conclusions

In normotensive patients, dexmedetomidine 0.7 μg/kg infusion prior to propofol induction effectively reduces the vagolytic effect of pancuronium before intubation but not after intubation, nor does it blunt the pressure responses to intubation. It also quickens the onset of pancuronium but does not affect the duration.

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ผลของยาเด็กซ์เมดิโทมิดีนต่อการออกฤทธิ์เวโกลัยติกของยาแพนคูโรเนียม ระหว่างการนำสลบด้วยยาโพรโพฟอล

วรวุธ ลาภพิเศษพันธุ์, ตันหยง พิพานเมฆาภรณ์, เฉลิมเกียรติ ตรีสุทธาชีพ และ กัญชนา วิเศษการ
ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

วัตถุประสงค์ ศึกษาผลของยาเด็กซ์เมดิโทมิดีน (Dexmedetomidine: Dex) ต่อการออกฤทธิ์เวโกลัยติกของยาแพนคูโรเนียม และต่อการตอบสนองทางระบบไหลเวียนเลือดในระหว่างการนำสลบและใส่ท่อช่วยหายใจในผู้ป่วยที่มีความดันเลือดปกติ รวมถึงผลต่อฤทธิ์หย่อนกล้ามเนื้อของยาแพนคูโรเนียม

วิธีการศึกษา ศึกษาในผู้ป่วยผู้ใหญ่ 44 ราย ที่มีความดันเลือดและจังหวะการเต้นของหัวใจปกติ แบ่งผู้ป่วยเป็น 2 กลุ่ม ๆ ละ 22 ราย กลุ่มควบคุม (group C) ได้รับน้ำเกลือนอร์มัล 20 มล. และกลุ่มศึกษา (group D) ได้รับยา Dex ขนาด 0.7 มคก./กก. เจือจางเป็น 20 มล. หยดทางหลอดเลือดดำก่อนการนำสลบด้วยยาโพรโพฟอลร่วมกับยาแพนคูโรเนียมขนาด 0.12 มก./กก. และใส่ท่อช่วยหายใจหลังจากนั้น 2.5 นาที วัดความดันเลือดซีสโตลิก (systolic blood pressure: SBP) ความดันเลือดไดอาสโตลิก (diastolic blood pressure: DBP) ความดันเลือดแดงเฉลี่ย (mean arterial pressure: MAP) และอัตราการเต้นของหัวใจ (heart rate: HR) ณ เวลาก่อนและหลังให้ยาศึกษา หลังให้ยาแพนคูโรเนียม 2.5 นาที ทันทีหลังจากใส่ท่อช่วยหายใจและหลังจากนั้นอีก 5 ครั้งห่างกันครั้งละ 1 นาที (T0-T5) วัดความไวการออกฤทธิ์ (onset) และระยะเวลาการออกฤทธิ์ (duration) ของยาแพนคูโรเนียมที่กล้ามเนื้อ adductor pollicis โดยเครื่อง TOF Watch

ผลการศึกษา หลังได้รับยาแพนคูโรเนียม 2.5 นาที Group D มี HR ต่ำกว่า Group C (75.7±9.3 vs 88±12.9 ครั้งต่อนาที p=0.013) แต่ไม่ต่างจากค่าควบคุม หลังใส่ท่อช่วยหายใจ HR ที่ T0-T5 ในทั้ง 2 กลุ่มไม่แตกต่างกัน ตลอดการศึกษา SBP, DBP และ MAP ในทั้ง 2 กลุ่มไม่แตกต่างกัน แต่ใน group C ณ เวลาก่อนใส่ท่อช่วยหายใจ SBP ต่ำกว่าค่าพื้นฐาน (106.4±12.0 vs 121.0±13.9 มม.ปรอท p=0.001) ขณะใส่ท่อช่วยหายใจร้อยละ 92.0 ของผู้ป่วยใน group D มี twitch height ของกล้ามเนื้อ adductor pollicis ที่น้อยกว่าร้อย 10 เปรียบเทียบกับร้อยละ 67.0 ของผู้ป่วยใน group C (p=0.048) ระยะเวลาการออกฤทธิ์ของยาแพนคูโรเนียมในทั้ง 2 กลุ่มไม่แตกต่างกัน

สรุปผลการศึกษา ในผู้ป่วยที่มีความดันเลือดปกติ การให้ยา Dex ขนาด 0.7 มคก./กก. หยดทางหลอดเลือดดำก่อนการนำสลบจะสามารถลดการออกฤทธิ์เวโกลัยติกของยาแพนคูโรเนียมในระหว่างการนำสลบด้วยยาโพรโพฟอลก่อนการใส่ท่อช่วยหายใจ แต่ไม่สามารถลดการตอบสนองของความดันเลือดที่เพิ่มสูงขึ้นต่อการใส่ท่อช่วยหายใจ นอกจากนี้ Dex ยังทำให้ยาแพนคูโรเนียมออกฤทธิ์เร็วขึ้นแต่ไม่มีผลต่อระยะเวลาการออกฤทธิ์
เชียงใหม่เวชสาร 2560;56(2):81-8.

คำสำคัญ: dexmedetomidine, pancuronium, vagolytic effect, intubation, hemodynamic responses