Abstract

Background: Sedation for colonoscopy with propofol is often associated with decreasing in arterial blood pressure. Dexmedetomidine is a sedative drug with a highly selective alpha2 adrenoreceptor agonist. The direct action on blood vessels causes vasoconstriction and a possible increase of blood pressure. This study evaluates dexmedetomidine on suppression of decrease in blood pressure compared with propofol for sedation during colonoscopy.

Method: Seventy patients with ASA physical status I-III were randomly allocated into two groups to receive either dexmedetomidine or propofol for elective colonoscopy under sedation. Group P patient received 0.5 mcg/kg fentanyl over 5 min, followed by 1 mg/kg propofol. Group D patients received 1 mcg/kg dexmedetomidine with 0.5 mcg/kg fentanyl over 5 min, followed by 20 mg propofol. The 20 mg propofol was titrated as required to achieve the target BIS and sedation score. Standard monitorization were provided in both groups before sedation (baseline), start of sedation (time=0) and every 5 min intervals.

Result: The incidence of hypotension in Group P was significantly greater than Group D (50% vs. 20%; P=0.015). The average doses of ephedrine used in Group P was more than Group D (4.0 mg vs. 0.8 mg; P=0.011). The systolic blood pressure in Group P was significant lower than that of Group D at 5th and 20th min after start of sedation while the heart rate in Group P was higher than Group D at 10th min and from 25th min throughout the period of colonoscopy (P=0.06). There were no statistically significant differences in the induction time, intraoperative bradycardia, postoperative complications and patient satisfaction between the two groups. The patients in Group P recovered from sedation more slowly than Group D (10.2 min vs. 6 min; P=0.038) and there were fewer patients in Group P who think that they can resume normal activities on the day of colonoscopy (63.3% vs. 86.6%; P=0.018).

Conclusion: Dexmedetomidine for sedation in colonoscopy reduced hypotension incidence than propofol.

Introduction

Nowadays colonoscopy is the standard procedure for diagnosis, screening, treatment and follow-up for many colorectal diseases. Although some patients can tolerate colonoscopy procedure without any sedation and analgesic requirements, it is a distressful procedure for most patients. As a result different techniques have been developed, and conscious sedation using propofol is most widely and frequently used due to its own pharmacokinetic and pharmacodynamics, i.e. fast onset, easy to titrate and rapid wake-up time [1,2].

Although propofol is widely used, it may cause bradycardia, respiratory depression and hypotension. Sedation with propofol is often associated with a significant decrease in arterial blood pressure especially in patients with advanced age, higher ASA (American Society of Anesthesiologist) physical status class-II and prior hypotension [3]. Hypotension is reported in 5-45% [4-7]. The mean reduction of systolic blood pressure is 21.1+-11.7 mmHg during propofol sedation for colonoscopy [8].

Dexmedetomidine is a well-known potent sedative agent. The pharmacologic profile preferred potential effects decrease in need for other anesthetics and analgesic drugs [9-12]. Dexmedetomidine produces dual alpha-2-adrenergic agonist and alpha-1-adrenergic antagonist actions on the human arteries [13]. Besides, its cardio protective effects and the direct action on blood vessels causing vasoconstriction and a possible increase in blood pressure [14]. At the therapeutic doses, the use of dexmedetomidine is not associated with respiratory depression [15]. It also has minimal adverse effects on respiratory functions even at high plasma dosages [16]. Because of these positive effects, it may be a valuable sedative for exploring the used of dexmedetomidine with small doses of propofol during colonoscopy was the possibility that adequate sedation could be provided with minimal hypotension.

Thus, the purpose of this study was to evaluate that dexmedetomidine could suppress the decrease in blood pressure during sedation in patients undergoing colonoscopy.

Materials and Methods

After the Institutional Review Board (IRB) approval and informed consent was obtained, from the subjects. 60 patients scheduled for elective colonoscopy under sedation were included in this prospective, randomized, double blinded, clinical study. Inclusion criteria were: adult, 20-79 years old with ASA physical status I-III. Exclusion criteria were: ASA physical status IV, cardiovascular disease such as arrhythmia, aortic and mitral stenosis, coronary artery disease, congestive heart failure, hypovolemia, shock, liver or renal insufficiency, uncooperative patient; allergy or previous adverse reaction to dexmedetomidine or propofol; the therapeutic doses, the use of dexmedetomidine is not associated with respiratory depression [15]. It also has minimal adverse effects on respiratory functions even at high plasma dosages [16]. Because of these positive effects, it may be a valuable sedative for exploring the used

*Corresponding author: Anchalee Techanivate, Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, E-mail: anchaleenivate12@hotmail.com

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propofol (soy bean, egg) or fentanyl, history of delayed emergence, high risk of airway obstruction, pregnancy and morbid obesity. The patients were randomly assigned into two groups by computer generation as Group D (n=30) for dexmedetomidine and Group P (n=30) for propofol. Randomly allocated coded syringes of the drugs were prepared by an anesthetist nurse who would not be involved in the intraoperative sedation and postoperative observation. Patients, anesthesiologists, endoscopists and postoperative observers were blinded to group allocated.

On arrival into the operating room, an IV catheter was placed into the left hand and normal saline solution was infused at 100 ml/h. The Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), Respiratory Rate, (RR), Oxygen Saturation (SpO₂), Bispectral Index (BIS) and Sedation By Alertness/Sedation (OAA/S) scale (Table1) were recorded as a baseline measurement, start of injection of the study drugs (time=0) and then every 5 minutes until they were transferred to the recovery room. Nasal inhalation of oxygen was given at 3 L/min and end tidal carbondioxide (ETCO₂) was obtained and through the whole procedure. To obtain and maintain a stable level of sedation or to treat discomfort, supplemental saline solution (total volume=10 ml).

The anesthesiologist started a stopwatch with the first administration of sedative medication. All times recorded were from the continuously running stopwatch and included the start of sedation (time=0:00); the time of colonoscopy insertion (OAA/S scale=3 with BIS<80); the time the colonoscopy was withdrawn from the anus; the time OAA/S scale=4 with BIS=90; and the time ready for home discharge. “Induction time” was defined as the total elapsed time between the start of sedation and colonoscopy insertion. “Recovery time” was defined as the total elapsed time between colonoscopy withdrawn and OAA/S scale=4 with BIS=90.

If hypotension (Systolic Blood Pressure (SBP) <30% of baseline level or<80 mmHg) occurred, 6 mg of ephedrine was administrated intravenously. In the event of bradycardia (HR<40 bpm), 0.6 mg of atropine was administrated.

At PACU, the recovery was assessed using the Modified Aldrete score system. The patient who achieved a Modified Aldrete score of nine or more was could then be discharged from PACU. Episodes of nausea, vomiting, hypotension (SBP<80% of baseline value), bradycardia (HR<50 beat/min) and delayed discharge time for more than 2h were recorded. Before discharge, the patients were being assessed about their satisfaction and amnesia by questionnaires (Table 2).

### Statistical analysis

Sample size calculation showed that approximately 30 patients would need to be recruited into each group to ensure a power of 80% and drop out of 10% to detect a different of VRS between the 2 groups. Allowing for the probability of a type 2 errors of 0.1 and type 1 error of 0.05, considered the reduction of hypotension incidence from 45% to 20%. The statistical analysis was carried out with SPSS version 17. Patient characteristics were expressed as mean (Standard Deviation, SD). Comparison between the two groups for numerical data was performed with independent sample t-test and within-group comparisons by the paired samples t-test. Nominal variables were compared by chi-square test. The data were given as the mean (Standard Deviation, SD), median (range) or numbers where appropriate. The P value<0.05 was considered statistically significant.

### Result

Sixty patients (23 males and 37 females) were included into this study. Thirty patients received propofol (Group P) and another thirty received dexmedetomidine (Group D). All patients were successfully completed colonoscopy procedure.

There were no significant differences between the groups regarding to age, sex, body weight, ASA physical status, diagnosis and baseline hemodynamic parameters (Table 3). The induction time (time between the start of sedation and colonoscopy insertion) and duration of colonoscopy were not different between the groups. After colonoscopy was withdrawn, patients in Group P took longer time to reach OAA/S scale=4 with BIS=90 than Group D (10.2 min vs. 6.0 min; P=0.038).

The incidence of hypotension in Group P was significantly higher than Group D (50% vs. 20%; P=0.015) (Table 4). From subgroup analysis, in the age group ≤ 60 years, the incidence of hypotension also showed similar result. But the patients in the age group>60 years, Group D showed greater tendency to develop hypotension and the incidence of hypotension in both groups was not significantly different. The onset

<table>
<thead>
<tr>
<th>Score</th>
<th>Reactivity</th>
<th>Speech</th>
<th>Face expression</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Clear</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic to name spoken in normal tone</td>
<td>Mild slowing</td>
<td>Mild relaxation</td>
<td>Mild ptosis</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is called loudly or repeatedly</td>
<td>Prominent slowing</td>
<td>Marked relaxation</td>
<td>Marked ptosis</td>
</tr>
</tbody>
</table>
| 2     | Responds only after mild prodding or shaking Few recognizable word | Does not respond after squeezing of the trapezius

Table 1: Alertness/Sedation (OAA/S) scale.
of hypotension was early in Group P than in Group D (10 min vs. 20 min; P=0.021). The lowest SBP in the propofol group was less than in the dexmedetomidine group (87.5 mmHg vs. 100.5 mmHg; P=0.013). There were two patients in Group P and one patient in Group D who developed bradycardia and atropine was given. The bradycardia in all the three patients occurred at 10 min after starting the study drugs. The lowest HR in the propofol group was not significantly different from the dexmedetomidine group.

The systolic blood pressure of both groups was significantly reduced from the baseline from the 5th minute after start sedation throughout the period of colonoscopy (P>0.05) (Figure 1) and the reduction was significantly less in patient receiving dexmedetomidine at the 5th minute and at the 20th minute (P<0.05).

Heart Rate (HR) in Group P was significantly reduced from the baseline at the time of starting the administration of the sedative drugs to 20th minute (P>0.05) (Figure 2) while HR in Group D was significantly reduced from the baseline following the starting of administration of the sedative drugs onwards till the end of colonoscopy (P>0.05) (Figure 2). Comparing between the groups, HR at 15th, 25th, 30th, 35th, 40th, and 45th minute were significantly higher in Group P than in Group D (P<0.05).

The mean dosage of ephedrine for the treatment of hypotension was statistically higher in Group P than in Group D (4.0 mg vs. 0.8 mg; P=0.011), but the mean dosage of atropine in both groups was not different. In Group P, the mean dosage of propofol required during colonoscopy was significantly higher than Group D (118 mg vs. 24.6 mg; P<0.001) (Table 5).

There were no differences in the respiratory endpoints between groups in the colonoscopy period. All patients maintained oxygen saturation, respiration rate, and end tidal carbon dioxide level. At PACU, the incidence of postoperative hypotension and bradycardia were insignificantly different between the study groups. Four patients (13.3%) in Group P and five patients (16.6%) in Group D had blood pressure less than 20% from their baseline value. One patient (3.3%) in Group P and two patients (6.6%) in Group D had heart rate lower than 50 bpm. The treatment was intravenous 200 ml normal saline fluid loading, 6 mg ephedrine in 1 case of Group P and 0.6 mg atropine in 1 case of Group D. No delayed discharge time longer than 2 hours.

From analysis of the postoperative questionnaires (Table 6), the satisfaction scores, the remembrance of the procedures were not different between the groups. Seven patients (23%) in Group P and 5 patients (17%) in Group D were recalled during the colonoscopy procedure with mild to moderate pain or discomfort. Nevertheless, the patient satisfaction score (range 1-10) to colonoscopy and sedation in both groups was high (9.3-9.6). Only regarding the question of the ability to resume normal activities after colonoscopy, there were more patients in the dexmedetomidine group thought that they could resume their normal activities (63.3% in Group P vs. 86.6% in Group D; P=0.018).

### Discussion

In Group P, we used 0.5 mcg/kg fentanyl infusion over 5 min plus bolus 1 mg/kg propofol before colonoscopy and Group D, we used 1 mcg/kg dexmedetomidine and 0.5 mcg/kg fentanyl infusion over 5
min plus bolus 20 mg propofol before colonoscopy. In both groups, additional 20 mg propofol IV bolus as required for achieve and maintain the level of sedation at BIS<80 with OAA/S scale ≤ 3 and if the patients had moans, movements, or grimaces. The additional propofol was monitored for the hypotension.

There was laboratory result that demonstrated a powerful inhibitory effect of propofol on sympathetic outflow [17]. Dexmedetomidine is also known to decrease sympathetic outflow and circulating catecholamine levels and would therefore be expected to cause the decrease of blood pressure and heart rate similar to those of propofol [18,19]. In our study, the systolic blood pressure was decreased from baseline in both groups from the 5th minute after starting the study drugs [18,19]. Therefore, systolic blood pressure at the 5th min in the propofol group was more decreased than in the dexmedetomidine group and the onset of hypotension was more early (10 min vs. 20 min).

From the figure of systolic blood pressure variables during the intraoperative period, the average blood pressure in the propofol group seem to be lower than in the dexmedetomidine group from the 5th to 20th minute. Then after the 20th minute, the average blood pressures in both groups were similarly and the statistic showed no difference. That means the vasoconstriction effect of dexmedetomidine may be last long as 20 minutes.

From subgroup analysis of the age group>60 years, patients in the dexmedetomidine group showed greater tendency to develop hypotension which was not different from the propofol group. This may explained by the fact that dexmedetomidine had worse effect on blood pressure in the elderly patients and should be more closely monitored for the hypotension.

Propofol has limited analgesic effect and higher doses are often required, when it is used as a single agent for colonoscopy, resulting in higher sedation levels. Thus, the use of propofol in combination with other agents may be preferable to propofol alone [20]. Leslie reported sympathectosis. Although there were reports that sleepiness appeared within 5 minutes after intravenous administration of dexmedetomidine and reached its maximum effect within 15 minutes [9] but the transient increase in blood pressure stared at one minute and peaked within 3 minutes [13]. Therefore, systolic blood pressure at the 5th min in the propofol group was more decreased than in the dexmedetomidine group and the onset of hypotension was more early (10 min vs. 20 min).

<table>
<thead>
<tr>
<th>Number of patients developed hypotension</th>
<th>Group P (n=30)</th>
<th>Group D (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (50%)</td>
<td>6 (20%)</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Age ≤ 60 yr</td>
<td>10/18 (55.5%)</td>
<td>3/18 (16.6%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Age &gt;60 yr</td>
<td>5/12 (41.6%)</td>
<td>3/12 (25%)</td>
<td>0.386</td>
</tr>
<tr>
<td>Onset of hypotension (min)</td>
<td>10 (5-40)</td>
<td>20 (5-60)</td>
<td>0.021</td>
</tr>
<tr>
<td>Lowest SBP (mmHg)</td>
<td>92.5 (66-142)</td>
<td>100.5 (69-127)</td>
<td>0.013</td>
</tr>
<tr>
<td>Lowest HR (beat/min)</td>
<td>55.5 (38-82)</td>
<td>54 (35-72)</td>
<td>0.077</td>
</tr>
</tbody>
</table>

Table 4: Incidence and onset of hypotension and bradycardia.

**Table 5: Drugs usage during colonoscopy.**

<table>
<thead>
<tr>
<th>Drugs usage during procedure value (mg)</th>
<th>Group P (n=30)</th>
<th>Group D (n=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>4.0 ± 5.5 (0-18)</td>
<td>0.8 ± 2.07 (0-6)</td>
<td>0.111</td>
</tr>
<tr>
<td>Atropine</td>
<td>0.04 ± 0.1 (0-0.6)</td>
<td>0.02 ± 0.1 (0-0.6)</td>
<td>0.557</td>
</tr>
<tr>
<td>Propofol</td>
<td>118 ± 118* (60-460)</td>
<td>24.6 ± 25.5 (0-80)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 6: The postoperative questionnaires.

Figure 2: Heart rate variables during the intraoperative period. * is statistically significant between two groups (P<0.05) ◆ is statistically significant from baseline (P<0.05)
a high incidence of hypotension in patients sedated with fentanyl and propofol for elective colonoscopy as in our study. Their report showed an incidence of hypotension (defined as a 25% or greater drop in systolic blood pressure from pre-sedation value) as 45% that was similar to our result in Group P [5]. Jolowiecki used dexmedetomidine in colonoscopy and observed 4/19 cases of hypotension (MAP=50% of baseline), 2 cases of bradycardia (HR=40 beats/min), 1 case of bigemini ventricular extra systole and 9 cases of pain that required additional opioids in the postoperative [21]. Their study was stopped before planned patients had been recruited because of bradycardia and hypotension. In our study, we did not detect severe hypotension or arrhythmia in the patients who received dexmedetomidine. We assumed that the differences in our hemodynamic values from the study of Jolowiecki had resulted from the difference of the sedatives, that used bolus 1 mcg/kg dexmedetomidine followed by 0.2 mcg/kg/h dexmedetomidine infusion without additional fentanyl. Because during stretching of colon and mesenteric attachments from the looping of colonicoscopic shaft, there have been report on vasovagal reaction in unseated patients [22]. It is possible that the pain may exacerbate more vagal reflex in Jolowiecki study. Also the difference of patient’s physical status, which we had lower number of ASA II-III cases 56% compared with 75% in the study of Jolowiecki.

Dexmedetomidine is also associated with decrease in heart rate because of its sympatholytic effect which is similar to the other sedatives and a baroreflex effect after vasoconstriction [19]. Kaygusuz compared the sedation with dexmedetomidine 1 mcg/kg, followed by 0.2 mcg/kg/h or propofol 1 mg/kg followed by 2.4 mg/kg/h during a shockwave lithotripsy combined with fentanyl 1 mcg/kg and reported no significant difference in heart rate values during sedation and recovery but the heart rates in each groups decreased from baseline [23]. The present study, Group D demonstrates a significant decrease in heart rate from baseline from the time starting the study drug throughout the period of colonoscopy (45 minutes) while the heart rate in Group P decreased from baseline for a short period (from the time starting the study drug to 20th minute). However, the average heart rate, lowest heart rate, the incidence of bradycardia and the atropine usage in our study were not significantly different between both groups during intraoperative and postoperative.

Dexmedetomidine has a long duration of sedative action that Muller reported prolonged recovery period in comparison with propofol [24]. However, we observed a better recovery in the dexmedetomidine group than in the propofol group with regard to a faster recovery period and higher percentage of the patients thought that they could resume their normal activities. The difference from the Muller study may have resulted from the longer mean duration time of colonoscopy in our study (24 and 42 minutes), the way we use a single dose of dexmedetomidine without continuous infusion and the use of propofol 20 mg as required for maintenance level of sedation in both groups. The result of the far difference in the mean dosage of propofol was required during colonoscopy between two groups (118 and 24.6 mg). This may confirm the characteristic of single dose dexmedetomidine in its ability to achieve sedation but preserve patient arousalness [25].

There are few limitations in our study, however. First, we used dexmedetomidine and supplementary propofol to maintain the level of sedation that might obscure the real effects of dexmedetomidine on the hemodynamics. The durations of colonoscopy varied from 15 minutes to more than 2 hr and procedure also varied. So this might impact the effect of dexmedetomidine because of many doses of propofol added in the longer cases. It would be important to note and select whether there was a difference in the frequency of the screening, polypectomy and other aggressive interventions between the two groups but the authors did not record them in detail. A further potential limitation is the difference in the onset time of action and the method of administration between propofol and dexmedetomidine that were difficult to measure the true induction time of the two drugs. Dexmedetomidine has slower onset of action and the method of administration is recommended in the technique of infusion that is difficult in the titration of the sedation when patient awakes, making movement or feeling uncomfortable. Propofol has a faster onset of action drug, so the usage of propofol in titration is fast and effective. Unlike, here who compared between dexmedetomidine and midazolam in sedation for colonoscopy; he reported that they had similar onset and duration times [26].

The position of colonoscopy is usually left side down, if the blood pressure was measure on the right arm, the measurement value is always 10-20 mmHg lower than the real blood pressure value included the baseline blood pressure that was measured at the first time in the supine position. It may be better if the arterial catheter is inserting, the transducer is adjusted at the right position, the zeroing is done and the direct arterial blood pressure is used in measurement. Otherwise, we did not assess the satisfaction of the endoscopists in technical difficulty for colonoscopy between the groups.

If the practitioner plans to introduce dexmedetomidine into everyday practice, the cost of this drug should be taken into account. Dexmedetomidine is still very expensive. At our hospital, a 2 ml vial of dexmedetomidine (200 mcg) cost 5 times more than a 20 ml ampule of propofol (200 mg). However, we believe that, under justified, for example, when administering sedation in patients with marginal cardiovascular function, further study on cost-effectiveness of dexmedetomidine in this kind of operation may be needed before concluding that it is appropriate to routinely use the drug for sedation in colonoscopy.

In conclusion, the present study demonstrate that 1 mcg/kg of dexmedetomidine added to 0.5 mcg/kg fentanyl and 20 mg propofol provides reduction in hypotension than 1 mg/kg propofol added to 0.5 mcg/kg fentanyl during colonoscopy. Furthermore, the use of dexmedetomidine has faster recovery time without increasing the rate of complications included bradycardia or delayed discharge time.

References

cardiorespiratory function in colonoscopy using midazolam combined with fentanyl or propofol. Int J Colorectal Dis 26: 703-708.


