□ 영문논문 □

Sedation with Propofol-Midazolam Combination versus Propofol alone during Spinal Anesthesia: Prospective, Randomized Study

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Background: Propofol can produce a dose-dependent reduction in blood pressure by providing titratable sedation and rapid recovery. It has been reported that a combination of midazolam and propofol resulted in the significant reduction in the total dose of propofol needed. It was hypothesized that the addition of low-dose midazolam to propofol may provide sufficient sedation without compromising the hemodynamic stability.

Methods: A total of 40 consecutive patients were randomly assigned to one of two groups (n = 20 each). Group M-P received a bolus of 0.02 mg/kg of midazolam, followed by a propofol infusion with a fixed target concentration of 1.0 μg/ml. Group P received only a propofol infusion with an initial target plasma concentration of 2.5 μg/ml. Subsequent titration of the infusion rates in Group P or the additional midazolam boluses in Group M-P were made in order to maintain a predetermined sedation level.

Results: In Group P, a mean dose of 5.4 ± 0.7 mg/kg/h propofol was used compared with 2.7 ± 0.5 mg/kg/h in Group M-P (P < 0.0001, plus additional 2.96 ± 1.8 mg of midazolam). Ephedrine was administered to 15 patients in Group M-P and 17 patients in Group P. Recovery was significantly fast (Group P, 6.8 ± 2.9 min vs. Group M-P, 9.8 ± 4.4 min, P < 0.05).

Conclusions: Sedation with propofol plus midazolam requires a lower total dose of propofol compared with propofol alone but has no superior hemodynamic stability. A further study using younger patients and combinations of different doses of each drug will be needed. **(Korean J Anesthesiol 2005; 49: S 10~3)**

Key Words: hypotension, midazolam, propofol sedation, spinal anesthesia.

INTRODUCTION

Drug combinations are used frequently in clinical anesthesia. As well as widening the spectrum of action of anesthesia, the use of combinations can also decrease side effects, mainly reducing the doses of individual drugs necessary via synergism.

Propofol is commonly used as a sedative by infusion during regional anesthesia.[1,2] Although propofol offers titratable sedation and rapid recovery, it can compromise hemodynamic stability. This may prove to be an important clinical consideration for its use as an adjunct to spinal anesthesia, as hypotension is a frequent complication of sympathetic blockade.

Midazolam is a popular adjuvant drug for intravenous anesthesia. It has been reported that midazolam and propofol act synergistically, and the combined application of both drugs results in the significant reduction in the total dose of propofol needed.[3-6]

Therefore, we believed that combination of a propofol-midazolam regimen might reduce the incidence of hypotension compared to propofol alone for sedation during spinal anesthesia. To our knowledge, the interactions of midazolam with propofol have not been studied for this aspect. We compared the requirements for vasopressor to maintain normotension to evaluate the hemodynamic stability between a propofol-midazolam combination and propofol alone as a sedative adjunct to spinal

anesthesia.

MATERIALS AND METHODS

After obtaining Institutional Ethics Committee approval and informed patient consent, ASA physical status I-II patients scheduled for elective total knee replacement arthroplasty were prospectively included in the study. Patients were allocated to one of two groups according to a randomized sequence.

On arrival in the operating room, standard monitoring was put in place. A crystalloid preload (lactated Ringer's solution, 7 ml/kg) was intravenously infused without premedication. A spinal anesthetic was performed at L4-5, with the patient in the lateral position. Hyperbaric bupivacaine (Marcaine® Spinal 0.5% Heavy, AstraZeneca, Sodertalje, Sweden) was administered in doses sufficient to provide a satisfactory sensory block for the procedure.

Those patients assigned to Group M-P (n = 20) received a bolus of 0.02 mg/kg of midazolam at 5 minutes after spinal anesthesia and then another 5 minutes later, a maintainance infusion using a Diprifusor Master TCI Infusion System (Fresenius Vial SA, France) started. This was programmed with the patient's weight and set to achieve a target plasma propofol concentration of 1.0 μg/ml. Group P (n = 20) patients received a continuous infusion of propofol with an initial target plasma concentration of 2.5 μg/ml at 10 minutes after spinal anesthesia. The level of sedation was recorded every 5 minutes, and subsequent dose alteration were made to maintain a predetermined level (Level 4 or 5) on a 5-point sedation score (Table 1).[7] To achieve the target sedation level, intermittent boluses of 0.02 mg/kg of midazolam was injected every 5 minutes without altering target concentration of propofol in Group M-P or target concentration of propofol was changed in Group P.

The baseline systolic arterial pressure was defined as the mean of systolic pressures taken at a ward. Ephedrine was administered in 5 mg increments if two successive measurements of the systolic arterial pressure had decreased below 0.80 times baseline.

Table 1. Sedation Scale

Sedation scale	Definition
1	Fully awake and oriented
2	Drowsy, eyes open
3	Drowsy, eyes closed but rousable
4	Drowsy, eyes closed, rousable on mild stimulation
5	Unrousable on mild physical stimulation

The propofol infusion was discontinued at the end of the surgical procedure (last skin suture), and the total drug requirements were noted. After the procedure, the time until the patient was fully alert (conversant and awake) and the propofol effect site concentration at the moment were registered.

All patients were visited 24 hours after their anesthesia and questioned about their satisfaction with the anesthetic technique used and recall of any specific events during operation. All side effects during sedation were recorded.

The data were analyzed using SPSS 10.0 (SPSS Inc., USA), and are presented as mean ± SD for laboratory values. The characteristics of the two groups were analyzed by using a two-tailed unpaired t-test. Statistical significance was accepted when P was < 0.05.

RESULTS

The two groups did not differ with respect to age, weight or height. There were no significant differences between the groups regarding final sensory block height achieved or total amount of infused crystalloid. Although the duration of anesthesia was shorter in Group M-P, it did not reach statistical significance (Table 2).

Sedation scores were practically identical for both groups, with a constant degree of sedation being maintained over time. The mean dose of propofol was significantly different between groups (2.7 ± 0.5 mg/kg/h in Group M-P vs. 5.4 ± 0.7 mg/kg/h in Group

Table 2. Patient and Procedural Characteristics

	Group P	Group M-P
Number	20	20
Age (yr)	67.2 ± 6.6	70.6 ± 7.3
Body weight (kg)	59.1 ± 10.8	58.4 ± 9.1
Height (cm)	153.1 ± 7.6	151.4 ± 6.0
Anesthetic time (min)	138.8 ± 22.7	128.0 ± 16.5
Total propofol (mg/kg/h)	5.4 ± 0.7	2.7 ± 0.5*
Required ephedrine (n)	17	15
Total ephedrine (mg)	12 ± 8.5	13.8 ± 13
Block level (dermatome)	T6 ± 2	T7 ± 2
Crystalloid infusion (ml/kg/h)	9.5 ± 3.0	11.3 ± 3.7
Awakening time (min)	6.8 ± 2.9	9.8 ± 4.4*
Effect site concentration of propofol (μg/ml)	1.5 ± 0.4	0.6 ± 0.2*

Data are presented as mean ± SD. *P < 0.05 compare to group P. Group P: Sedation with propofol, Group M-P: Sedation with propofol plus midazolam.
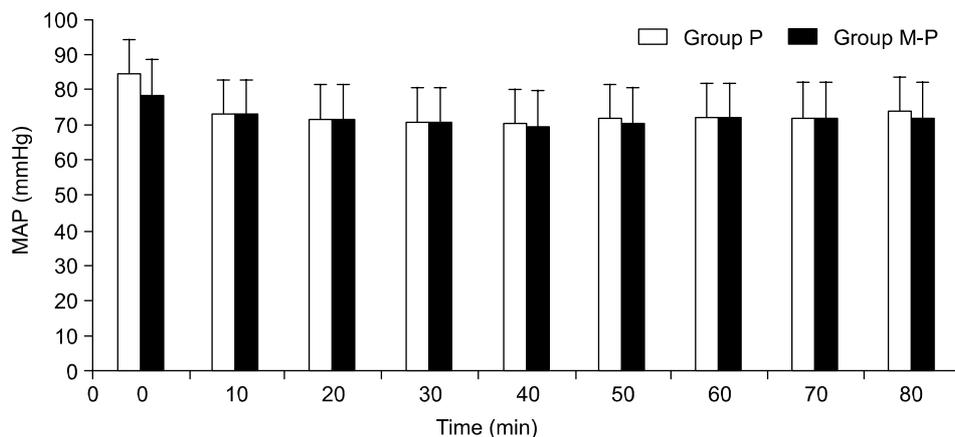
Fig. 1. This graph shows changes of mean arterial pressure during the first 80 minutes after initiation of sedation. The differences between the both groups are not statistically significant. Data are presented as mean ± SD. Group P: Sedation with propofol, group M-P: Sedation with propofol plus midazolam. MAP: mean arterial pressure.

P, P < 0.0001). Mean arterial pressures were similar in the two groups during operation (Fig. 1). Additional midazolam was administered in 13 patients of Group M-P and the mean dose was 2.96 ± 1.8 mg (range, 1 -7.5). Ephedrine was given in 15 patients of Group M-P and in 17 patients of Group P, respectively (P > 0.05). The requirements for supplemental ephedrine were similar for both groups (Group M-P, 13.8 ± 13 mg, Group P, 12 ± 8.5 mg).

The mean time until the patient was fully alert after the operation was 6.8 ± 2.9 min (range, 1-10 min) in the patients with propofol-sedation alone (Group P) but 9.8 ± 4.4 min (range, 3-17 min) in those patients under sedation with propofol plus midazolam (Group M-P, P < 0.05). The mean propofol effect site concentration when the patient was alert was also significantly higher in the Group P (1.5 ± 0.4 μg/ml, range 0.8-2.2 μg/ml) compared to Group M-P (0.6 ± 0.2 μg/ml, range 0.3-1.3 μg/ml, P < 0.0001).

All patients expressed their satisfaction regarding the anesthetic technique chosen and didn't recall any intraoperative events.

DISCUSSION

While our data confirm the previous anaesthesiological results that the individual dose requirement for propofol can be significantly lowered with the combination of propofol plus midazolam, it failed to show that synergism between propofol and midazolam rendered better hemodynamic stability.

It is possible that our failure to show a hemodynamic stability was due to the large dose of propofol given, which resulted in a larger reduction of arterial pressure, or the characteristics of our study patients who were old, therefore sensitive to the effects of propofol.

The drug requirements for sedation were quite variable according to the target sedation level. The mean propofol dose we used to maintain sedation level 4 or 5 on a 5-point sedation score was 5.4 mg propofol/kg/h and it was comparable with other study which maintained same sedation level for monitored anesthesia care.[8] In another study which propofol administration was titrated to effect level 3 on a 5-point sedation score, the mean propofol dose was 1.4 mg.[9] In the same study, ephedrine was administered after more than 25% reduction in mean arterial pressure from baseline and ephedrine was given only 35% of total patients compared to 85% of ours. The large dose of propofol, despite midazolam combination, might produce hypotension because propofol causes dose-related cardiovascular depression. As a synergistic or other interaction may be apparent only within specific dose ranges of the two agents.[10] it is important to vary the doses of both groups and study different range of drug combinations.

The mean age of our patients was over 65 yr with the range 56 to 86 years. The older the patients are, the more they can develop hemodynamic depression with propofol. Numerous pharmacokinetic studies have shown that the clearance of propofol is significantly decreased, the volume of distribution remains unchanged and blood propofol concentration increases and decreases more rapidly in the elderly compared with younger populations.[11-13]

In addition, pharmacodynamic study has shown that the elderly have an increased sensitivity to the effects of propofol.[14] Propofol also has a more dramatic effect on haemodynamic function in the elderly. The blood concentration of propofol associated with a 50% drop in systolic blood pressure was lower in patients 70-85 years of age compared with those 20-39 years of age.[15]

While the sedation efficacy was rated similarly in both groups,

the mean recovery time was significantly short under sedation with propofol alone than with propofol plus midazolam. Although three-minute difference is statistically significant, we consider its clinical significance is negligible.

Present study clearly demonstrates that the combination of propofol and midazolam requires a lower total dose of propofol compared to propofol alone, but otherwise has no superior hemodynamic stability. We recognize that work with respect to younger age group and different range of drug combinations would be of value.

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