Brief Clinical Reports

Midazolam premedication reduces propofol requirements for sedation during regional anesthesia

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Purpose: Propofol is often used for sedation during spinal anesthesia. We investigated the effects of midazolam premedication on the propofol requirements and incidence of complications during sedation.

Methods: In a prospective randomized, controlled, and single-blinded study, 50 patients undergoing elective gynecological surgery were randomly divided into control and midazolam groups. Patients in the midazolam group received 2 mg midazolam *im* 30 min before arrival at the operation room. After spinal anesthesia was instituted with intrathecal injection of hyperbaric tetracaine, we provided sedation using continuous infusion of propofol. The level of sedation was controlled at a level between "eyes closed but rousable to command" and "eyes closed but rousable to mild physical stimulation" by adjusting the infusion rate. During sedation, the propofol requirements and complications were recorded and patients were asked, two hours after the end of operation, whether they remembered intraoperative events.

Results: In the midazolam group, the loading dose, steady state infusion rate, and overall infusion rate of propofol were $0.74 \text{ mg}\cdot\text{kg}^{-1}$, $2.86 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$, and $3.32 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$, respectively, which were about 17% lower than those in the control group ($P < 0.05$). Moreover, midazolam premedication reduced the incidence of intraoperative memory ($P < 0.05$), but had no effects on other complications.

Conclusion: Midazolam premedication reduced propofol requirements and the incidence of intraoperative memory during sedation. These effects on sedation using propofol during spinal anesthesia are considered beneficial for patients.

Objectif : Le propofol est souvent utilisé pour la sédation pendant la rachianesthésie. Nous avons exploré les effets de la prémédication avec du midazolam sur les besoins en propofol et sur l'incidence de complications pendant la sédation.

Méthode : Lors d'une étude prospective, randomisée, contrôlée et à simple insu, 50 patientes pour qui une intervention gynécologique avait été prévue ont été réparties de façon aléatoire en un groupe témoin et un groupe midazolam. Les patientes du groupe midazolam ont reçu 2 mg de midazolam *im*, 30 min avant l'arrivée en salle d'opération. Après la mise en route de la rachianesthésie avec une injection intrathécale de tétracaïne hyperbare, nous avons administré la sédation par une perfusion continue de propofol. La sédation a été contrôlée à un niveau se situant entre le moment où les patientes ont «les yeux fermés mais peuvent être éveillées sur commande» et le moment où elles ont «les yeux fermés mais peuvent être éveillées sous une légère stimulation physique», en ajustant la vitesse de perfusion. Pendant la sédation, les besoins de propofol et les complications ont été notés et on a demandé aux patientes, deux heures avant la fin de l'opération, si elles se rappelaient des événements peropératoires.

Résultats : Dans le groupe midazolam, la dose de charge, la vitesse de perfusion à l'état d'équilibre et la vitesse globale de perfusion du propofol ont été de $0,74 \text{ mg}\cdot\text{kg}^{-1}$; $2,86 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ et $3,32 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, respectivement, mesures qui sont de 17 % plus basses que celles du groupe témoin ($P < 0,05$). De plus, la prémédication avec du midazolam a réduit l'incidence de rappel peropératoire ($P < 0,05$), mais n'a pas eu d'effet sur d'autres complications.

Conclusion : La prémédication avec du midazolam a réduit les besoins de propofol et l'incidence de souvenir de la période peropératoire pendant la sédation. Ces effets sur la sédation utilisant le propofol pendant la rachianesthésie sont considérés comme bénéfiques pour le patient.

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Accepted for publication 24 September 1999.

S PINAL anesthesia with adequate sedation is often employed for lower abdominal surgery. Propofol is a useful drug for providing sedation during regional anesthesia.^{1,2} However, it may also cause dose-dependent cardiovascular and respiratory depression.

Because synergistic interactions between midazolam and propofol have been reported,^{3,4} we assumed that midazolam premedication would reduce propofol requirements and the incidence of complications during sedation. The aim of this study was to examine this assumption.

Patients and methods

The Hospital Ethics Committee approved this study and informed consent was obtained from 50 patients undergoing elective gynecological laparotomy under spinal anesthesia. Criteria for entry into this study were ASA physical status I or II, age 25-65 yr., and no recent prescription of psychotropic medication. The patients were randomly divided into control and midazolam groups according to the computer generated random number. In the control group, patients received no premedication and in the midazolam group patients received 2 mg midazolam *im* as premedication 30 min before arrival at the operating room.

On arrival in the operating room, an intravenous line was secured and all patients were monitored with ECG, noninvasive automatic blood pressure and pulse oximetry. After baseline measurements, an epidural catheter was placed at L₂₋₃ interspace for postoperative analgesia. Then, spinal anesthesia was instituted with an intrathecal injection of 2.5 or 3 ml of tetracaine 0.4% and glucose 10% via a 25 gauge needle through L₃₋₄, and analgesia was obtained to the Th4 level.

After placing a small sampling tube in the nasal vestibule to monitor respiratory rate and expired carbon dioxide partial pressure, sedation was started. Propofol was infused at a rate of 3 mg·kg⁻¹·hr⁻¹, and 10 mg bolus injections at three minute intervals were added until response to verbal command diminished or disappeared. Thereafter the infusion rate was adjusted to maintain a sedation score of 3 or 4 (Table I).¹ Infusion of propofol was stopped at the end of the operation. The loading dose (LD dose), steady state infusion rate (SS rate), and overall infusion rate (OA rate) of propofol were recorded to compare the requirement between the groups. The definition of these indices were as follows; LD dose was the dose administered until response to verbal command diminished or disappeared, SS rate was the infusion rate when steady state sedation level was obtained, and OA rate was the value divided total dose of propofol during sedation by sedation time.

TABLE I Sedation score

Score	Degree of sedation
1	Fully awake and orientated
2	Drowsy
3	Eyes closed but rousable to command
4	Eyes closed by rousable to mild physical stimulation (earlobe tug)
5	Eyes closed but unrousable to mild physical stimulation

TABLE II Demographic data, propofol requirements, and cases of intraoperative complications

	Control group (n=25)	Midazolam group (n=25)
<i>Demographic data</i>		
Age (yr)	47.7 ± 8.7	46.3 ± 9.9
Weight (kg)	53.7 ± 7.3	55.1 ± 7.8
Duration of anesthesia (min)	107.8 ± 27.4	104.5 ± 25.8
Duration of surgery (min)	68.3 ± 27.2	69.5 ± 28.8
<i>Propofol requirements</i>		
LD dose (mg·kg ⁻¹)	0.89 ± 0.28	0.74 ± 0.16*
SS rate (mg·kg ⁻¹ ·hr ⁻¹)	3.47 ± 0.91	2.86 ± 0.76*
OA rate (mg·kg ⁻¹ ·hr ⁻¹)	3.98 ± 1.00	3.32 ± 0.86*
<i>Cases of complication</i>		
Intraoperative memory	7	1*
Intraoperative dream	2	5
Uncontrolled movement	2	4
Application of oxygen	22	25
Apnea	11	13
Vomiting	1	0
Airway obstruction	7	8
Securing a patent airway	6	8
Pressor use	11	13

**P* < 0.05

Ephedrine (4 mg *iv*) was administered when blood pressure was < 80% of baseline level, and 0.25 mg atropine was injected when heart rate was < 45 min⁻¹. Supplemental oxygen was given when SpO₂ was < 95%. Apnea was defined that absence of expired CO₂ and respiratory movement were > 15 sec.

The level of sedation and the complications such as transient apnea, uncontrolled movement, administration of ephedrine or atropine, and supplemental oxygen requirement were also recorded. Two hours after the end of sedation, patients were asked if they had dreamed or remembered intraoperative question about nausea and pain.

Continuous data were summarized using mean ± SD and analyzed using the unpaired t test. Discrete data were reported as numbers and analyzed using a chi-square test. A value of *P* < 0.05 was considered statistically significant.

Results

Both groups were similar in age, weight, height, duration of the surgery and sedation, and distribution of disease. Propofol requirements in the midazolam group were lower than in the control group ($P < 0.05$) (Table II). Midazolam premedication reduced the LD dose, SS rate, and OA rate to 83.1%, 82.4% and 83.4% compared with those of the control group, respectively.

During sedation, the blood pressure and heart rate slightly decreased and gradually returned to the baseline level at 50 min after the start of propofol infusion in both groups.

The baseline SpO_2 value in the midazolam group was lower than in the control group ($P < 0.05$), but there was no case that SpO_2 was $< 96\%$. Although SpO_2 decreased $< 94\%$ in both groups during induction, it was easy to manage this desaturation using supplemental oxygen.

Midazolam premedication reduced the incidence of intraoperative memory, but had no effect on the incidence of the other complications (Table II).

Discussion

In this study, the propofol requirement for inducing sedation in the midazolam group was 16.9% lower than in the control group. It is controversial whether midazolam reduces the dose of propofol to induce anesthesia. Small amounts of midazolam (1-4 mg *iv*) administered two to four minutes prior to propofol infusion can reduce the propofol requirement for induction of anesthesia.^{3,4} On the contrary, 30 $\mu\text{g}\cdot\text{Kg}^{-1}$ midazolam administered immediately before induction did not reduce the induction dose of propofol.⁵ The main factor, which influenced these results, was the interval between midazolam and propofol injections. It has been reported that *t*-max of intramuscular administrated midazolam is approximately 30 min.^{6,7} Thus, 2 mg midazolam *im* 30 min before arrival at the operation room could obtain nearly maximum effect of premedication and reduce induction dose of propofol.

Midazolam premedication also reduced propofol requirement to maintain sedation. Two previous reports were unable to detect any effect of midazolam on propofol requirement for maintaining sedation or anesthesia.^{5,8} Propofol requirement for maintenance was larger than that in our study, that is, deeper sedation level was required in those studies. We speculated that 2 mg midazolam could reduce propofol for maintenance only when the level of sedation was controlled as light as we selected.

Although midazolam premedication could not reduce sedation induced circulatory and respiratory

depression; midazolam premedication could reduce intraoperative memory. As memories of intraoperative events may cause patient discomfort, this effect is considered beneficial.

In conclusion, midazolam premedication reduces propofol requirements for sedation, increases the incidence of intraoperative amnesia, and has no effect on the incidence of other complications. Thus, midazolam premedication is helpful as a sedation adjunct to spinal anesthesia using with propofol.

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