Oral clonidine premedication reduces induction dose and prolongs awakening time from propofol-nitrous oxide anesthesia

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Purpose: To evaluate whether oral clonidine premedication affects the induction dose of propofol and awakening time from epidural and propofol anesthesia.

Methods: Thirty-nine female patients (ASA I or II) were randomly allocated to receive 5 $\mu g \cdot kg^{-1}$ clonidine *po* or no clonidine 90 min before induction of anesthesia. After epidural anesthesia was achieved with lidocaine, general anesthesia was induced with continuous *iv* infusion of propofol at a rate of 50 $mg \cdot min^{-1}$ until loss of eyelash reflex and responses to verbal commands, which were judged by a blinded observer. After a laryngeal mask airway was inserted, anesthesia was maintained with N_2O 67%, O_2 33% and propofol adjusted to maintain hemodynamic stability. After completion of surgery, a blinded observer recorded the time from discontinuance of propofol and N_2O until the patient was awake and responsive (awakening time), and then, the laryngeal mask airway was removed.

Results: The induction dose of propofol in the clonidine group (1.4 ± 0.3 mg) was less than that in the control group (1.9 ± 0.4 mg, $P < 0.05$), while the awakening time of the clonidine group (470 ± 145 sec) was longer than that of the control group (329 ± 123 sec, $P < 0.05$).

Conclusion: Premedication with 5 $\mu g \cdot kg^{-1}$ clonidine *po* reduced the induction dose of propofol, but delayed emergence from propofol anesthesia.

Objectif : Déterminer si la clonidine orale administrée comme prémédication affecte la dose d'induction de propofol et le temps de réveil lors d'une anesthésie péridurale combinée à une anesthésie générale au propofol.

Méthode : Trente-trois patientes (ASA I ou II) ont été réparties au hasard et ont reçu 5 $\mu g \cdot kg^{-1}$ de clonidine *po*, ou n'ont pas eu de clonidine, 90 min avant l'induction de l'anesthésie. L'anesthésie péridurale étant réalisée avec de la lidocaïne, l'anesthésie générale a été induite avec une perfusion *iv* continue de propofol selon un débit de 50 $mg \cdot min^{-1}$ jusqu'à la disparition du réflexe ciliaire et des réponses aux commandes verbales, jugée par un observateur impartial. L'anesthésie a été maintenue, après l'insertion d'un masque laryngé, avec N_2O 67 %, O_2 33 % et du propofol ajusté au maintien de la stabilité hémodynamique. À la fin de l'intervention, un observateur objectif a noté le temps écoulé depuis l'arrêt du propofol et de N_2O jusqu'au moment où la patiente était éveillée et pouvait réagir (temps de réveil), puis, on a enlevé le masque laryngé.

Résultats : La dose d'induction de propofol dans le groupe clonidine (1,4 ± 0,3 mg) a été plus faible que dans le groupe témoin (1,9 ± 0,4 mg, $P < 0,05$), et le temps de réveil dans le groupe clonidine (470 ± 145 sec) a été plus long que dans le groupe témoin (329 ± 123 sec, $P < 0,05$).

Conclusion : La prémédication avec 5 $\mu g \cdot kg^{-1}$ de clonidine *po* a réduit la dose inductive de propofol, mais a retardé le réveil après l'anesthésie au propofol.

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LONIDINE is associated with delayed emergence from anesthesia using intravenous,[1] and volatile agents,[2] at least in part, due to a decreased MAC-awake.[2,3] Propofol provides a smooth induction of, and rapid emergence from general anesthesia as well as a postoperative antiemetic effect.[4] As a result, propofol is increasingly used in ambulatory anesthesia, for which prolonged recovery is not desirable. The interaction between clonidine and propofol has not been well defined. Previous reports demonstrated that oral clonidine did not affect the induction dose of propofol,[5,6] while it decreased the maintenance dose of propofol.[5] More importantly, it has not been determined whether clonidine prolongs the awakening time from propofol anesthesia as is seen with volatile anesthetic agents.[2]

This study was designed to evaluate the effects of oral clonidine premedication on; 1) induction and maintenance doses of propofol, and 2) awakening time from propofol-nitrous oxide anesthesia in combination with continuous epidural analgesia in healthy patients.

Methods

Following approval from our Institutional Research Committee and informed patient consent, 39 ASA I or II patients undergoing elective gynecological surgery were studied. Patients were randomly assigned to clonidine group (n = 19) receiving approximately 5 $\mu g \cdot kg^{-1}$ clonidine plus 20 mg famotidine *po*, or control group (n = 20) receiving 20 mg famotidine alone 90 min before arrival in the operating room.

Electrocardiography and noninvasive blood pressure cuff were applied. Lactated Ringer's solution was infused at a rate of 10 $ml \cdot kg^{-1} \cdot hr^{-1}$ during the course of the study. An epidural catheter was placed at L_{1-2} or L_{2-3} interspace, and 15 ml lidocaine 1.5% with epinephrine (1:200,000) was injected. To alleviate pain associated with *iv* propofol, 3 ml lidocaine 2% *iv* was first administered, and general anesthesia was induced 30 sec later with propofol at a rate of 50 $mg \cdot min^{-1}$ (300 $ml \cdot hr^{-1}$) *iv* until loss of eyelash reflex and response to verbal commands determined at 10-sec interval observed by a blinded observer. Infusion of propofol was temporarily terminated, and the amount given was recorded. A laryngeal mask airway was inserted without any other adjuvant, and increments of 40 mg propofol were given as necessary. After insertion of laryngeal mask airway, patients were allowed to breathe spontaneously. Anesthesia was maintained with N_20 67%, O_2 33% and propofol at a rate of 8 $mg \cdot kg^{-1} \cdot hr^{-1}$ for 10 min, 6 $mg \cdot kg^{-1} \cdot hr^{-1}$ for 10 min and 4 $mg \cdot kg^{-1} \cdot hr^{-1}$ until the completion of surgery. During surgery, the infusion rate of propofol was adjusted between 4 and 8 $mg \cdot kg^{-1} \cdot hr^{-1}$ to maintain systolic blood pressure ± 20% of baseline values, which was taken as the resting measurement on the day before surgery. In addition, 10 ml lidocaine 1.5% with epinephrine were given hourly through the epidural catheter. Hypotension (systolic blood pressure < 70% of baseline value) was treated by 5 mg ephedrine *iv*. Bradycardia (heart rate < 50 $beats \cdot min^{-1}$) was treated with atropine. After the completion of surgery, propofol and N_2O were discontinued. A blinded observer removed the laryngeal mask airway when the patient was able first, to breathe spontaneously and maintain $P_{ET}CO_2$ between 35 and 45 mmHg; and second, to open her eyes on command. The time from the discontinuance of propofol and N_2O until the removal of the laryngeal mask airway was recorded as awakening time.

The results are expressed as mean ± SD, and were analysed with unpaired Student's t test or *chi*-squared test. Awakening times were compared using Kaplan-Meier survival method. A P value < 0.05 was considered statistically significant.

Results

There were no differences between groups in terms of demographic, surgical and anesthetic data (Table). The induction dose of propofol in the clonidine group was less than that in the control group, while maintenance doses of propofol were comparable between groups. Awakening time in the clonidine group was longer than that in the control group. Also, median value of awak-

TABLE Demographic, anesthetic and surgical data

	Control group (n=20)	*Clonidine group (n=19)*
Age (yr)	44 ± 9	44 ± 7
Weight (kg)	58.0 ± 9.5	55.2 ± 6.1
Height (cm)	157 ± 6	155 ± 4
Duration of surgery (min)	105 ± 31	109 ± 34
Duration of anesthesia (min)	150 ± 31	152 ± 35
Total dose of lidocaine (mg)	472.5 ± 88.5	477.0 ± 84.0
Dose of propofol ($mg \cdot kg^{-1}$)		
At induction	1.9 ± 0.4	1.4 ± 0.3*
After induction before incision†	2.7 ± 0.2	2.7 ± 0.3
During surgery	7.0 ± 0.2	7.7 ± 0.6
Awakening time (sec)	329 ± 123	470 ± 145*

Values are mean ± SD

† Average times between the induction of anesthesia and the surgical incision were 29 and 25 min in the control and the clonidine groups, respectively.

After the induction of anesthesia, propofol was infused at 8 $mg \cdot kg^{-1} \cdot hr^{-1}$ for 10 min, 6 $mg \cdot kg^{-1} \cdot hr^{-1}$ for 10 min, and 4 $mg \cdot kg^{-1} \cdot hr^{-1}$ for the remainder until the incision.

* $P < 0.05$ *vs* the control group.

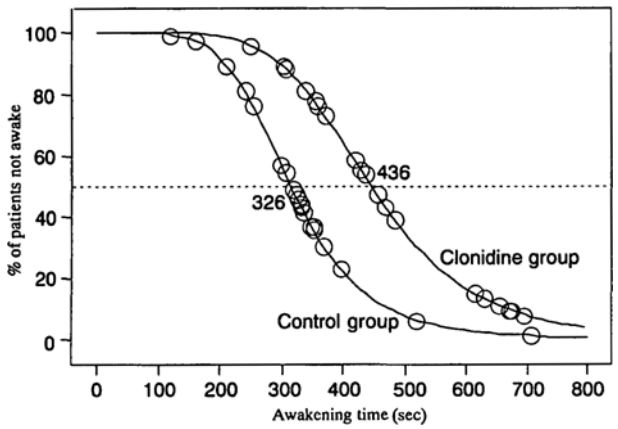

FIGURE Percentages of patients who were not awake as a function of time from the discontinuance of propofol and N_2O. Patients in the clonidine group received 5 $\mu g \cdot kg^{-1}$ clonidine *po* 90 min before induction of general anesthesia (n = 19), and those in the control group received no clonidine (n = 20). Awakening time in the clonidine group was longer than that in the control group ($P < 0.05$).

ening time in the clonidine group was longer than that in the control group (Figure). Eighteen and 15 patients developed hypotension, and received ephedrine during surgery in the control and clonidine groups, respectively, but none developed bradycardia.

Discussion

When 5 $\mu g \cdot kg^{-1}$ clonidine *po* given as premedication the induction dose of propofol was reduced, but the awakening time from combined epidural-general anesthesia using propofol plus nitrous oxide was prolonged. The reduced induction dose of propofol in the clonidine-treated patients is considered as an additive hypnotic effect of clonidine, although previous reports gave controversial results regarding the induction dose of *iv* agents.[5-9] On the other hand, the prolongation of recovery by clonidine is consistent with previous reports, in which recovery from isoflurane,[2] or alfentanil-propofol anesthesia[1] was delayed. Since plasma concentrations of propofol were not measured in our study, it is not clear whether prolonged recovery in clonidine-treated patients is explained by pharmacokinetic and/or pharmacodynamic interaction between clonidine and propofol, or clonidine and nitrous oxide. However, a delayed emergence of 2.5 min as seen in our study, may not be of serious clinical importance.

There were some limitations in our study. First, the dosing regimen of propofol with a fixed lowest rate may have overestimated the true requirement of propofol during surgery.[5] Use of a BIS monitor, for instance, would have helped to control the anesthesia depth more strictly and to determine the anesthetic requirement more precisely. Thus, we cannot exclude the possibility that clonidine-treated patients received a larger dose of propofol than was necessary to attain unconsciousness with effective epidural analgesia. Second, we did not assess the degree of sedation postoperatively. Prolonged awakening time observed in our study may be reflected in delayed recovery of psychomotor function. However, postoperative recovery of psychomotor performance was reported previously not to be delayed in patients given 150 µg clonidine compared with 1 mg flunitrazepam.[4]

In conclusion, premedication with 5 $\mu g \cdot kg^{-1}$ clonidine *po* reduced the induction dose of propofol, but prolonged recovery from epidural-propofol-nitrous oxide anesthesia.

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