ORIGINAL ARTICLE

The effect of pretreatment with clonidine on propofol consumption in opium abuser and non-abuser patients undergoing elective leg surgery

Morteza Jabbari Moghadam, Davood Ommi, Alireza Mirkheshti, Mehdi Shadnoush, Ali Dabbagh
Anesthesiology Research Center, Department of Anesthesiology, Shahid Beheshti University of Medicine, Tehran, Iran

Objective: Clonidine, an alpha-2 adrenergic agonist, increases the quality of perioperative sedation and analgesia with a few side effects. This study was designed to assess the effect of clonidine premedication on the anesthesics used for elective below knee surgeries in opium abusers and non-abusers. **Materials and Methods:** In a randomized clinical trial, 160 patients were selected and assigned into four groups. Eighty patients among the opium abusers were divided randomly into clonidine and no clonidine groups, with 40 patients in each, and 80 among the non-abusers were again divided randomly into clonidine and no clonidine groups, with 40 patients in each group. All were anesthetized for elective orthopedic operation using the same predetermined method. The total administered dose of propofol and other variables were compared. **Results:** The total propofol dose in a decreasing order was as follows: Abuser patients receiving placebo (862 ± 351 mg), non-abuser patients receiving placebo (806 ± 348 mg), abuser patients receiving clonidine (472 ± 175 mg), and non-abuser patients receiving clonidine (448 ± 160 mg). Hence, a statistically significant difference was observed among the four study groups (*P* value for ANOVA = 0.0001). **Conclusion:** Adding clonidine as a preoperative medication decreases the patient's anesthetic needs; this decrease was even more considerable on the anesthetic needs than the effect of opium abuse history on anesthetic dose.

Key words: Clonidine, elective surgery, opium abuse, propofol

INTRODUCTION

Acute pain management is one of the most challenging areas for anesthesiologists.[1,2] Different pharmacologic and non-pharmacologic methods have been used to overcome this problem.[3] There are a number of drugs that, when are administered before the operation, could decrease the severity of postoperative pain. Clonidine is one of these agents.

Clonidine is a natural alpha-2 adrenergic agonist. This drug can pass the blood–brain barrier and reach the central nervous system (CNS), where it can affect the CNS by decreasing the brain sympathetic tone, which would result in a drop in diastolic and systolic blood pressure measurements and also decreased heart rate. [1-3] In addition, clonidine has peripheral effects, which could lead to temporary and short-term increase in blood pressure values.[3-5]

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There are a number of studies well demonstrating that oral clonidine as a pretreatment to anesthesia can increase the quality of perioperative sedation and analgesia while having just a few side effects.[6-8] These beneficial effects of clonidine have been demonstrated not only in adult patients, but also in children[4] and in patients undergoing general anesthesia,[1] for neuraxial block[5,6] and nerve blocks.[9] Much more sophisticated investigations are under way for assessment of the effects of clonidine at the cellular level.[10] Therefore, we now consider clonidine as an agent far beyond the older antihypertensive drug[7-9,11,12] and clonidine is used for many anesthetic purposes.

It has been demonstrated that opium abuser patients are more sensitive to pain and need higher doses of anesthetics during the perioperative period.[13-16] This is due to a number of complex cellular and sub-cellular mechanisms that cause decrease the tolerance of these patients.[14,16]

This study was performed to assess the effect of clonidine premedication on the level of anesthesia and the total consumption of propofol for elective below knee surgeries in opium abuser and non-abuser patients.

MATERIALS AND METHODS

The study was performed after Institutional Review Board approval was obtained regarding ethical

Address for correspondence: Dr. Ali Dabbagh, Anesthesiology Research Center, Shahid Beheshti University of Medicine, Tehran, Iran.
E-mail: alidabbagh@yahoo.com
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considerations, at Shahid Beheshti University of Medical Sciences, Tehran, Iran. The study was also registered in the Iranian Clinical Trials Center (IRCT201202159026N1).

In a single-blinded, randomized clinical trial, among the total patients who were candidates for elective leg orthopedic surgery, we selected 160 patients and assigned them into the study groups. Then, we selected 80 patients among the opium abusers and 80 patients among the non-abuser patients. We did this selection according to the patients' responses during the preoperative visit performed by one of the authors; then, they were grouped in the clonidine or placebo groups according to the computer table of random numbers. The patients were blinded regarding the study group, while the physicians were not, making it a single-blinded study.

The sample size was determined after a power analysis considering $\alpha = 0.05$ and $\beta = 0.10$. Finally, 160 patients were considered as the study sample size which was divided into four groups with 40 patients in each.

Then, the 80 opium abuser patients were randomly assigned into one of the two groups, either receiving or not receiving clonidine. In addition, the 80 patients who were non-abusers were randomly assigned into one of the two groups (40 in each), again either receiving or not receiving clonidine.

These were the study inclusion criteria:
1. Patient giving informed written consent for entering the study
2. American Society of Anesthesiologists (ASA) classification score 1 or 2 (I or II)
3. Systolic blood pressure during the 48 h before surgery between 90 and 140 mmHg
4. Maximum length of surgery up to 120 min
5. Age range of 18–65 years
6. Any clinical cardiac arrhythmias before the operation
7. Preoperative saturation of oxygen by pulse oximetry above 90%

The exclusion criteria were:
1. Any history of egg sensitivity
2. Unstable hemodynamic status during the perioperative period
3. Multiple trauma or multiple fractures

The patients were anesthetized for elective orthopedic operation using the same predetermined method, including standard monitoring, the same dosage of drugs per kilogram body weight, and the same fluid therapy protocol. The depth of anesthesia was controlled and kept constant using the combination of the anesthetics. The anesthesia depth was monitored using CSM (Danmeter®, Denmark) which recorded crude EEG and the depth of anesthesia based on CSI. In addition, during the course of anesthesia, the anesthesiologist in charge of the patient detected the level of anesthesia by recording the bispectral index (BIS index) and controlled it to keep the value between 40 and 60. If any deviation of the BIS index was noted higher than this range, the level of anesthesia was corrected to reach the determined range using incremental supplements of propofol.

Finally, after termination of the surgery, one of the colleagues recorded the results for these variables: The length of operation, the detailed BIS number recordings, the total administered dose of propofol (calculated after induction dose), the length of anesthesia, and the patients' demographic findings.

Using SPSS (vers ion 11.5; SPSS Inc, Chicago, IL, USA), the data were entered and analyzed. For statistical data analysis, Student's *t* test, Chi-square test, and analysis of variance (ANOVA) were used. A value for *P* less than 0.05 was considered significant.

RESULTS

The results of the study demonstrated no significant difference among the four study groups regarding age, body weight [Table 1], gender [Table 2], the time of anesthesia, and the time of recovery stay [Table 3]. In addition, the results of anesthesia level monitoring showed no difference between the two groups regarding the BIS levels [Table 3 and Figure 1]. Nevertheless, there was statistically significant difference among the study groups regarding the total propofol dose [Table 3 and Figure 2].

The total propofol dose in a decreasing order was as follows: Abuser patients receiving placebo (862 ± 351 mg), non-abuser patients receiving placebo (806 ± 348 mg), abuser patients receiving clonidine (472 ± 175 mg), and non-abuser patients receiving clonidine (448 ± 160 mg). Hence, a statistically significant difference was observed among the four study groups (*F* value for ANOVA = 0.0001).

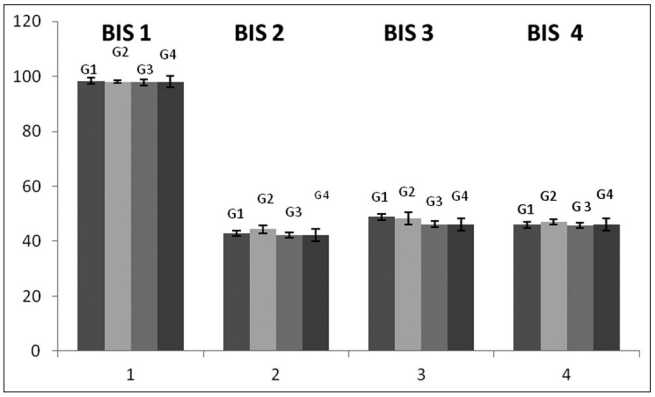

Figure 1: BIS numbers compared in each time interval in the study groups (mean ± SEM). BIS values are grouped as: BIS 1: BIS on admission; BIS 2: BIS during induction; BIS 3: BIS after intubation; BIS 4: BIS 10 min after intubation (G1: group 1; G2: group 2; G3: group 3; G4: group 4)

DISCUSSION

The results of this study suggest that adding clonidine as a preoperative medication decreases the patient's anesthetic needs; this result was demonstrated as there was a decreased need for propofol, despite the controlled level of anesthesia monitored using BIS index. The effect of this decreased need was even more considerable on the anesthetic needs than the effect of opium abuse history on anesthetic dose. Therefore, the results demonstrated that after using clonidine as a pretreatment, there is a considerable decrease in the use of anesthetic.

There are other studies considering the effect of clonidine use on anesthetic needs, which have demonstrated the effectiveness of the drug.[1-4] In addition, there are studies demonstrating the effect of chronic opium abuse on the anesthetic needs;[8-10] however, there are not many studies comparing the effects of receiving or not receiving clonidine in opium abusers and non-abusers. In one study,[11] premedication with oral gabapentin and clonidine were compared regarding hyperdynamic response after laryngoscopy and intubation, while our study considered induction of anesthesia and was continued all over the process – before the induction of anesthesia, during induction, and up to 10 min after the induction of anesthesia when the operation was started.[4] Therefore, this study was much more exact compared to the other similar study[4] regarding the timing of measurements and the method of anesthesia depth assessment. Another study confirmed the effect of oral clonidine on bleeding in endoscopic sinus surgery, which could decrease the need for fentanyl and hydralazine consumption,[12] while we did not measure this effect; instead, we compared the effect of clonidine on anesthetic consumption.

Clonidine has been used for a very long time in the clinical practice. But these days, we see an increasing trend of using it not just as an antihypertensive agent, but also as an anesthetic adjuvant.[1-2] Since clonidine is mainly an alpha-2 adrenergic agonist, it was used originally as an antihypertensive drug; but later on, it stared to be used as an adjuvant anesthetic, which is nowadays administered orally or through intravenous line or as an intrathecal agent. Clonidine can pass through the blood–brain barrier and reach the target central alpha-2 adrenoceptors where it could exert its effect on the CNS by suppression of the brain sympathetic tone. This is exactly the mechanism by which it could decrease the systolic and diastolic blood pressure and also the heart rate.[4-7] But clonidine does not only use the pathway of central alpha-2 adrenoceptor agonist, but could also affect the neuronal pathways during its administration as an adjuvant for spinal or epidural anesthesia, while many peripheral effects of the drug have been previously described.[3,8-10]

Table 1: Demographic variables*

	Group 1	Group 2	Group 3	Group 4	*F* value for ANOVA test**
Age	34.6 (14.6)	38.7 (12.4)	36.2 (13.1)	39.1 (11.3)	0.34
Weight	71.1 (13.1)	71.6 (11.6)	73.9 (10.3)	72.8 (10.3)	0.68

*Group 1: non-abuser patients receiving placebo; group 2: abuser patients receiving placebo; group 3: non-abuser patients receiving clonidine; group 4: abuser patients receiving clonidine **P* value for ANOVA

Table 2: Gender distribution in the study groups*

	Group 1	Group 2	Group 3	Group 4	*P* value for Chi-square test**
Female	18	17	19	20	0.04
Male	22	23	21	20	

*Group 1: non-abuser patients receiving placebo; group 2: abuser patients receiving placebo; group 3: non-abuser patients receiving clonidine; group 4: abuser patients receiving clonidine **P* value for Chi-square test

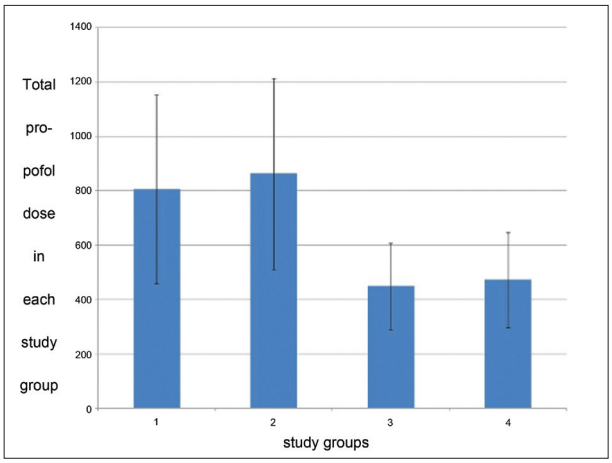

Figure 2: Total propofol dose in each of the study groups (mean ± SEM) (groups are as given in Tables 1–3)

Table 3: Study variables and their analysis results*

	Group 1	Group 2	Group 3	Group 4	*P* value for ANOVA test**
Duration of anesthesia	110.7 (27)	111.7 (33)	109 (24)	108 (36)	0.78
Stay in recovery	25.9 (5.3)	26.7 (8.4)	28.7 (6.7)	27.7 (7.3)	0.61
Total propofol dose	806 (348)	862 (351)	448 (160)	472 (175)	0.000
BIS on admission	98.4 (0.6)	98.1 (1.4)	97.8 (2.1)	98.1 (0.9)	0.37
BIS during induction	42.9 (2.2)	44.3 (2.6)	42.1 (1.6)	42.2 (2.6)	0.28
BIS after intubation	48.8 (4.2)	48.3 (4.1)	46.2 (4.2)	46.1 (3.9)	0.51
BIS 10 min after intubation	45.9 (4.1)	47.1 (3.9)	45.7 (3.7)	46.1 (4.1)	0.33

*Group 1: non-abuser patients receiving placebo; group 2: abuser patients receiving placebo; group 3: non-abuser patients receiving clonidine; group 4: abuser patients receiving clonidine **P* value for ANOVA

When we administer oral clonidine just a few hours or a few minutes before anesthesia, the quality of analgesia and sedation during the perioperative period would increase without significant side effects,[3-6] with results similar to our findings. These beneficial clonidine effects are seen in both adults and children.[4] In addition, the use of clonidine as an adjuvant anesthetic is not specific just for general anesthesia, but also there are studies that have used clonidine in neuraxial block administration,[5-7] during nerve blocks,[8] and in chronic intractable pain after thoracotomy.[9] Although it was possible to use clonidine for our patients in intrathecal route or administer it combined with nerve blocks, we wanted to check the effects of clonidine on total intravenous usage of propofol as an intravenous anesthetic, which could demonstrate interesting results. Our study could be more important, especially when we consider that there was no previous study comparing the effect of clonidine regarding the history of opium abuse.

Also, the decrease in anesthetic drug needs after clonidine pretreatment can result in both decreased costs and decrease in the possible complications after cumulative effects of the drug. Therefore, clonidine is a safe drug with minimal costs.

However, the mechanism of action of clonidine in its peripheral and neuraxial uses might be through inhibition of tetrodotoxin-sensitive sodium channels, besides its usual alpha-2 adrenoceptor agonistic effects.[10]

There are a number of limitations in our study. First, we had a predominance of male gender, although it was not statistically significant. However, the male/female ratio was higher in the abuser patients. So, the extrapolation of the results to the total female population is not possible. The second issue is that patient allocation was done after history taking. In other words, there was no lab data demonstrating the history of opium abuse; of course, taking the rights and welfare of the patients into consideration, we did not do any kind of lab exams to prove the history of opium abuse. Anyway, we allocated the patients according to their own history and we are not able to prove ethically the history of opium abuse. Finally, we did not check the postoperative effects of clonidine, while it could have sedation effects after the operation.

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REFERENCES

1. Cao JP, Miao XY, Liu J, Shi XY. An evaluation of intrathecal bupivacaine combined with intrathecal or intravenous clonidine in children undergoing orthopedic surgery: A randomized double-blinded study. Paediatr Anaesth 2011;21:399-405.
2. Bajwa SJ, Kaur J, Bajwa SK, Bakshi G, Singh K, Panda A. Caudal ropivacaine-clonidine: A better post-operative analgesic approach. Indian J Anaesth 2010;54:226-30.
3. Ghodki PS, Sardesai SP, Thombre SK. Evaluation of the effect of intrathecal clonidine to decrease shoulder tip pain in laparoscopy under spinal anaesthesia. Indian J Anaesth 2010;54:231-4.
4. Batra YK, Rakesh SV, Panda NB, Lokesh VC, Subramanyam R. Intrathecal clonidine decreases propofol sedation requirements during spinal anesthesia in infants. Paediatr Anaesth 2010; 20:625-32.
5. Yamama Y, Nishikawa K, Funao T, Mori T, Asada A. Intrathecal gabapentin and clonidine synergistically inhibit allodynia in spinal nerve-ligated rats. Life Sci 2010;87:565-71.
6. Ghatak T, Chandra G, Malik A, Singh D, Bhatia VK. Evaluation of the effect of magnesium sulphate vs. clonidine as adjunct to epidural bupivacaine. Indian J Anaesth 2010;54:308-13.
7. Kroin JS, Buvanendran A, Williams DK, Wagenaar B, Moric M, Tuman KJ, *et al.* Local anesthetic sciatic nerve block and nerve fiber damage in diabetic rats. Reg Anesth Pain Med 2010;35:343-50.
8. Xie HG, Cao YJ, Gauda EB, Agthe AG, Hendrix CW, Lee H. Clonidine clearance matures rapidly during the early postnatal period: A population pharmacokinetic analysis in newborns with neonatal abstinence syndrome. J Clin Pharmacol 2011;51:502-11.
9. Ayad AE, El Masry A. Epidural steroid and clonidine for chronic intractable post-thoracotomy pain: A pilot study. Pain Pract 2012;12:7-13.
10. Maruta T, Nemoto T, Satoh S, Kanai T, Yanagita T, Wada A, *et al.* Dexmedetomidine and clonidine inhibit the function of Na(v)1.7 independent of α(2)-adrenoceptor in adrenal chromaffin cells. J Anesth 2011;25:549-57.
11. Montazeri K, Kashefi P, Honarmand A, Safavi M, Hirmanpour A. Attenuation of the pressor response to direct laryngoscopy and tracheal Intubation: Oral clonidine vs. oral gabapentin premedication. J Res Med Sci 2011;16 Suppl 1: S377-86.
12. Jabalameli M, Hashemi M, Soltani H, Hashemi J. Oral clonidine premedication decreases intraoperative bleeding in patients undergoing endoscopic sinus surgery. J Res Med Sci 2005; 1:25-30. 25
13. Azarasa M, Azarfarin R, Changizi A, Alizadehasl A. Substance use among Iranian cardiac surgery patients and its effects on short-term outcome. Anesth Analg 2009;109:1553-9.
14. Vosoughian M, Dabbagh A, Rajaei S, Maftuh H. The duration of spinal anesthesia with 5% lidocaine in chronic opium abusers compared with nonabusers. Anesth Analg 2007;105:531-3.
15. Dabbagh A, Dahi-Taleghani M, Elyasi H, Vosoughian M, Malek B, Rajaei S, *et al.* Duration of spinal anesthesia with bupivacaine in chronic opium abusers undergoing lower extremity orthopedic surgery. Arch Iran Med 2007;10:316-20.
16. Dabbagh A, Moghadam SF, Rajaei S, Mansouri Z, Manaheji HS. Can repeated exposure to morphine change the spinal analgesic effects of lidocaine in rat? J Res Med Sci 2011;16:1361-5.

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