

Premedication effect of melatonin on propofol induction dose for anesthesia, anxiety, orientation and sedation after abdominal surgery: a double-blinded randomized trial

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Abstract

The present study addressed the effect of melatonin premedication on propofol induction dose for anesthesia in abdominal surgery. This is a double-blinded clinical trial in which abdominal surgery patients admitted to the Valiasr Hospital, Iran ($n=88$) were enrolled and individually randomized into two groups: melatonin and placebo groups sublingually administered 3 mg of melatonin and placebo, respectively, 50 minutes before surgery. Their anxiety, orientation, and sedation were recorded before melatonin administration, anesthesia induction, and recovery, while we also recorded the propofol induction dose required for general anesthesia. Anxiety was seen less in the melatonin group than the placebo group ($P < 0.05$), whereas orientation was significantly different before anesthesia induction ($P = 0.044$) and sedation was the same before the induction ($P = 0.044$) and recovery ($P = 0.049$) in both groups, with a better efficiency in the melatonin group in which a lower dose of propofol was used ($P = 0.002$). The sedation, anxiety, and propofol dose used were lower in the melatonin group than the placebo group. The recommended dosage was 3 mg of melatonin once to achieve an anesthetic depth index or a bispectral index of 40. The study was approved by Ethical Committee of Arak University of Medical Sciences with IR.ARAKMU.REC.1395.432 code in July 2016, and the trial was registered in Iranian Registry of Clinical Trials with IRCT20141209020258N98 in September 2016.

Key words: abdominal surgery; anesthesia; induction; melatonin; premedication; propofol

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INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone naturally produced in the brain, secreted by the pineal gland,¹ whose receptors are found throughout the central nervous system and other body tissues.^{2,3} It is known to be an effective hormone in sleep disorders,^{4,5} anxiety, and pain, as well as an anti-inflammatory antioxidant,⁶ used as a premedication.^{3,6,7}

Melatonin interacts with multiple receptors, including opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, $\alpha 1$ - and $\alpha 2$ -adrenergic, and melatonergic receptors found in the spinal cord in the central nervous system.^{3,8} Premedication reduces the need for anesthetic induction agents during surgery.^{7,9} Melatonin, an effective hypnotic drug, is revealed to have the effect on both the onset and maintenance of sleep,¹⁰ while it is known as a natural hypnotic agent whose actions are activated by MT1 and MT2 receptors and a yet-unclarified physiologic mechanism underlying the analgesic actions of melatonin.^{7,9}

Several studies have been focused on the effects of various premedication on the induction and maintenance propofol dose in the human body.¹¹ A dose range of melatonin premedication is used to provide sedation and analgesia without cognitive impairment and psychomotor skills, and without any increase in recovery time.^{5,12} Past studies have proven that melatonin is effective in the premedication of adults and children.¹³⁻¹⁵

Anderson et al.'s review⁷ which explored 24 clinical trials and 1749 participants suggested that melatonin decreases anxiety and pain, as compared to placebo. They performed three studies on anesthetic induction dose which reduced anesthetic dose but did not affect sevoflurane dose.⁷ While Turkistani et al.'s study¹⁶ suggested that melatonin 3 or 5 mg is recommended to reduce propofol dose to achieve bispectral index (BIS) 45, another which conducted on BIS and reducing the dose of anesthetic drugs by Evagelidis et al.'s study¹⁷ focused on the effect of melatonin premedication on the reduced administration of sevoflurane guided by BIS monitoring, reporting no effect on the reduction of anesthetic dose.

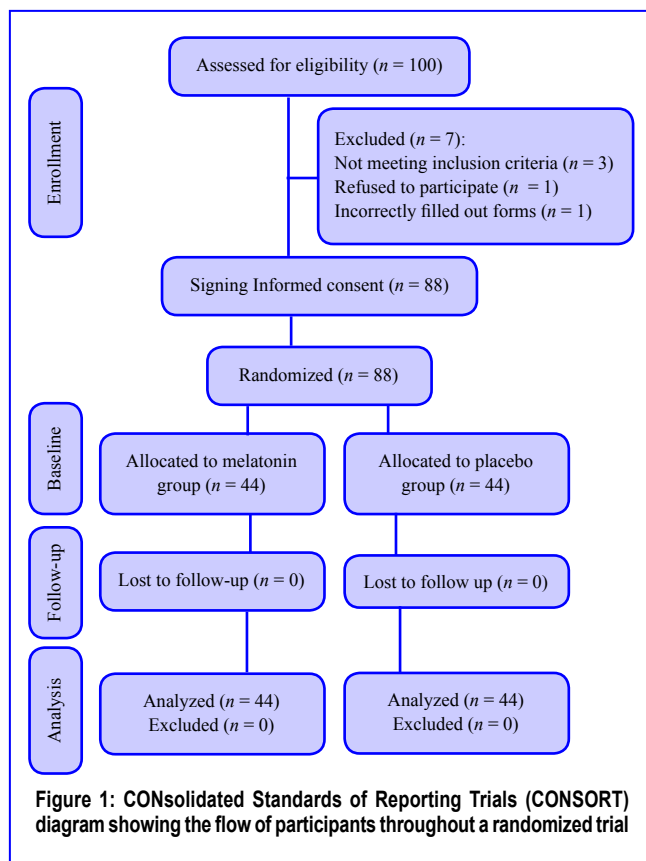
Melatonin-mediated analgesic effects may be involved in two melatonin receptors, γ -aminobutyric acid receptor, and opioid receptors.^{5,7,18} Melatonin can increase β -endorphins levels in the receptor MT2 in spinal cord and is effective as a premedication due to the sedative, hypnotic, analgesic, anti-inflammatory, anti-oxidative and chronobiotic properties.¹⁸ The review has revealed that melatonin is effective as a premedication in adults, but with controversial anesthetic effects.¹⁸ Premedication with sublingually and orally administered melatonin (0.05, 0.1, or 0.2 mg/kg) has been proven to reduce anxiety and to provide problem-free sedation in surgery and psychomotor skill test, or a negative impact on the quality of recovery.^{14,19} Ismail and Mowafi²⁰ studied the effect

of orally administered melatonin 10 mg as a premedication at 90 minutes before cataract surgery and found that it provided better operating conditions, including decreased intraocular pressure and enhanced analgesia, and it was also effective in reducing the pain caused by injuries.

However, there are few quantitative studies addressing melatonin premedication for reducing the dose of anesthetic agent used during surgery,^{16,19} whereas in Naguib et al.'s trial,¹⁹ 45 patients undergoing various surgeries received melatonin 100 minutes prior to surgery and only sufficed for eyelash reflex and verbal command, but in the present study we intended to perform, BIS was also used. Contrarily, the studies are limited and cannot be generalized to the entire community, while not considering all in each case, and the subject still needs to be reviewed. Thus, we designed a study to compare the effect of melatonin *versus* placebo as the premedication on propofol induction dose for anesthesia in abdominal surgeries in Arak, Iran.

SUBJECTS AND METHODS

This is a double-blinded clinical trial in which abdominal surgery patients admitted to the Valiasr Hospital, Iran ($n = 88$) were included after completing the informed consent form. The patients were informed about the objectives of study and signed the informed consent form. Moreover, the protocol of study was approved by the Ethical Committee of Arak University of Medical Sciences with IR.ARAKMU.REC.1395.432 code in July 2016. In addition, it was registered in Iranian Registry of Clinical Trials with IRCT20141209020258N98 in September 2016. The flow chart is shown in **Figure 1**.



The inclusion criteria included American Society of Anesthesiologists status I–II, age 15–55 years, non-emergency abdominal surgery, both genders, surgery time from 30 minutes to 1 hour and a half, body mass index > 19 to < 25 kg/m², and non-use of narcotics during the previous week. Exclusion criteria were including lack of patient cooperation and use of benzodiazepine-derived drugs within the past 72 hours.

Subjects were randomized into two groups: melatonin group ($n = 44$), sublingually administered 3 mg of melatonin (Webber, Naturals, Canada) dissolved in 3 mL of distilled water 50 minutes before surgery; and placebo group ($n = 44$), administered placebo (3 mL of distilled water) 50 minutes before surgery. The treatment was implemented by an anesthesiologist resident who was blinded to drugs. A nurse anesthetist prepared anesthetics and provided them with the resident. Afterwards, the subjects were transferred to the operating room, while recording vital signs, including oxygen saturation (SaO₂), and attaching the BIS monitor to him/her. The monitor electrodes were placed on three points: the middle of the forehead above the glabella, upper corner of the left eye, and left mastoid region.

Midazolam (Boroujerd Eksir Co, Broujerd, Iran) 0.2 mg/kg and fentanyl (Rasht Caspian Co., Iran), 2 µg/kg were injected into both groups, and then the induction of general anesthesia propofol Lipuro (B. Braun Medical) 1 mg/kg was started by the anesthesiologist resident and finally continued until the BIS reached 40. The total propofol dose was recorded to achieve the BIS to lose eyelash reflex and to prevent response to verbal stimulation. Then atracurium (Rasht Caspian Co., Iran) 0.5 mg/kg was injected and anesthesia continued by isoflurane, and nitrogen-oxygen (at 50:50), as well as and fentanyl injected at an appropriate dose for the time of surgery.

Anxiety, orientation and sedation were recorded before melatonin administration, before anesthesia induction and during recovery by the resident who then recorded mean arterial pressure (MAP), heart rate (HR), SaO₂, and end-tidal carbon dioxide (EtCO₂) before induction, every 10 minutes during and after surgery, and every 15 minutes after arrival in the recovery room until achieving a score of > 8 on the Aldrete scoring²¹ when the monitoring device was attached to the end of a nasal mask. Visual Analogue Scale score was used to assess patients' anxiety^{17,18} and then was completed by the resident. A 10 cm ruler was used to assess anxiety, in which zero stood for no anxiety and 10 stood for a severe anxiety.

Orientation scoring was based on: No orientation (0), orientation about place where patient is located (1), and orientation in both time and place (2).¹⁴ The sedation scoring was as follows: Awake (1), drowsy (2), asleep, but arousable (3), and asleep and not arousable (4).¹⁴ It should be noted that the data were measured by an anesthesiologist resident, unaware of the groupings, to double-blinded the study and then data were analyzed using descriptive and analytical statistics through SPSS 20 (IBM Corp., Armonk, NY, USA). Independent *t*-test and chi-square test were used in data analysis.

RESULTS

This double-blinded clinical trial was conducted in abdominal surgery patients ($n = 88$) admitted to the Arak Valiasr Hospital,



who were randomly assigned to two groups with a minimum age of 24 years, a maximum age of 55 years, and a mean age of 43.97 ± 7.40 years. No significant difference was seen in age between two groups ($P = 0.568$) who were matched for age. They showed no significant difference in gender ($P = 0.856$) and were gender matched.

Table 1: Baseline characteristics of abdominal surgery patients

Item	Melatonin (n = 44)	Placebo (n = 44)	P-value
Age (year)	43.34±7.69	44.25±7.16	0.568
Sex (male/female)	21/23	22/22	0.586
Time to surgery (minute)	89.25±12.5	91.18±15.45	0.435

Note: Data in age and time to surgery are expressed as the mean ± SD, and analyzed by independent t-test; and data in sex are expressed as number, and analyzed by chi-square test. Melatonin group: administered 3 mg of melatonin at 50 minutes before surgery; placebo group: administered 3 mL of distilled water at 50 minutes before surgery.

Based on the results in **Table 2**, a significant difference was found in MAP between the groups at 10, 20 and 70 minutes, and recovery time ($P < 0.05$). The MAP level was lower in the melatonin group than in the placebo group at all times. Based on the below chart, the lowest MAP is related to the melatonin group, whereas MAP had also a sharp increase in the placebo group at the time of extubation, but is low in the melatonin group. **Figure 1** shows the repeated measurement analysis for trend of MAP between two groups. Melatonin caused lower MAP in patients for all times.

Table 2: Comparison of mean arterial pressure (mmHg) between the patients in melatonin and placebo groups

	Melatonin (n = 44)	Placebo (n = 44)	P-value
Before anesthesia induction	78.60±68.04	79.80±75.02	0.183
10 minutes post-operation	74.60±22.32	76.80±31.48	0.007
20 minutes post-operation	73.60±22.33	76.70±73.04	0.041
30 minutes post-operation	74.02±6.18	76.27±7.61	0.084
40 minutes post-operation	73.50±52.93	76.70±65.95	0.082
50 minutes post-operation	73.60±25.95	76.80±25.49	0.140
60 minutes post-operation	74.50±43.0	76.70±97.03	0.95
70 minutes post-operation	74.50±21.70	76.70±23.93	0.016
80 minutes post-operation	74.50±40.34	77.70±20.39	0.023
90 minutes post-operation	76.50±47.87	77.60±50.82	0.292
After tracheal extubation	76.50±84.76	80.70±61.05	0.283
Recovery	76.50±73.04	77.70±79.51	0.040

Note: Data are expressed as the mean ± SD, and analyzed by independent t-test. Melatonin group: administered 3 mg of melatonin at 50 minutes before surgery; placebo group: administered 3 mL of distilled water at 50 minutes before surgery.

Based on **Table 3**, no statistically significant difference was seen in HR between the two groups ($P < 0.05$). Though no statistically significant difference was between them, the HR was lower in the melatonin group. Moreover, the repeated measurement test showed that no difference was observed in HR, but it was lower in the melatonin group ($P > 0.05$).

Table 3: Comparison of heart rate (beats/min) between the patients in melatonin and placebo groups

	Melatonin (n = 44)	Placebo (n = 44)	P-value
Before anesthesia induction	85.13±6.41	86.40±7.49	0.711
10 minutes post-operation	79.72±6.12	80.63±7.11	0.732
20 minutes post-operation	77.63±6.26	79.20±6.79	0.263
30 minutes post-operation	76.93±5.66	78.65±6.70	0.195
40 minutes post-operation	77.56±5.90	78.95±6.82	0.311
50 minutes post-operation	77.72±5.95	78.81±6.89	0.429
60 minutes post-operation	77.60±12.02	78.60±70.72	0.217
70 minutes post-operation	77.60±68.01	78.60±56.53	0.510
80 minutes post-operation	77.50±77.84	78.60±70.97	0.397
90 minutes post-operation	78.60±88.0	79.60±56.98	0.625
After tracheal extubation	83.50±59.34	83.70±50.50	0.984
Recovery	79.60±31.89	80.70±77.77	0.356

Note: Data are expressed as the mean ± SD, and analyzed by independent t-test. Melatonin group: administered 3 mg of melatonin at 50 minutes before surgery; placebo group: administered 3 mL of distilled water at 50 minutes before surgery.

Based on **Table 4**, there was a significant difference in SaO₂ between the groups after recovery and the mean of SaO₂ was higher in melatonin than placebo group. But there was no significant between two groups in other time after operation. **Figure 2** shows the trend of SaO₂ in two groups. Moreover, no significant difference was found in mean of EtCO₂ between groups ($P < 0.05$; **Figure 3**).

Table 4: Comparison of oxygen saturation (SaO₂) (mmHg) between the patients in melatonin and placebo groups

	Melatonin (n = 44)	Placebo (n = 44)	P-value
Before anesthesia induction	96.23±1.27	96.23±1.27	0.990
10 minutes post-operation	97.36±1.03	97.73±1.01	0.101
20 minutes post-operation	97.84±1.05	97.63±1.34	0.430
30 minutes post-operation	97.65±1.21	97.73±1.24	0.746
40 minutes post-operation	97.84±1.19	97.63±1.39	0.464
50 minutes post-operation	97.88±0.99	98.00±1.09	0.612
60 minutes post-operation	97.86±0.95	97.97±1.10	0.608
70 minutes post-operation	97.65±1.03	98.00±0.98	0.117
80 minutes post-operation	97.61±0.96	98.02±0.97	0.072
90 minutes post-operation	97.56±1.16	97.97±0.92	0.052
After tracheal extubation	96.77±1.44	96.79±1.43	0.941
Recovery	97.22±1.15	97.93±0.99	0.003

Note: Data are expressed as the mean ± SD, and analyzed by independent t-test. Melatonin group: administered 3 mg of melatonin at 50 minutes before surgery; placebo group: administered 3 mL of distilled water at 50 minutes before surgery.

Based on the results depicted in **Table 5**, no significant difference was seen in anxiety between both before melatonin administration ($P = 0.07$), but it was significantly different between in both groups before the induction ($P = 0.013$) and in recovery ($P = 0.034$) and less in the melatonin group.

In addition, no significant difference was found in orientation between both before melatonin administration and in recovery ($P > 0.05$), while it was statistically significant before anes-

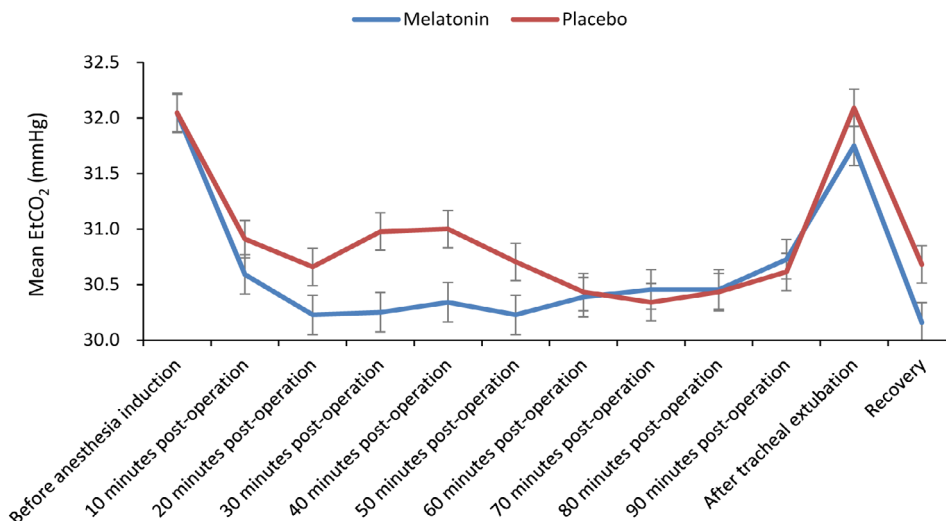


Figure 2: Comparison of mean end-tidal carbon dioxide (EtCO₂) between patients in melatonin and placebo groups
 Note: Data are expressed as the mean ± SD, and analyzed by independent *t*-test. Melatonin group: administered 3 mg of melatonin at 50 minutes before surgery; placebo group: administered 3 mL of distilled water at 50 minutes before surgery.

Table 5: Comparison of anxiety, orientation, sedation and propofol dose between the patients in melatonin and placebo groups

	Melatonin (n = 44)	Placebo (n = 44)	P-value
Anxiety			
Before melatonin administration	6.15±1.42	6.06±0.04	0.070
Before anesthesia induction	5.29±1.75	6.65±0.37	0.013
Recovery	2.13±0.82	2.75±1.03	0.034
Orientation			
Before melatonin administration	1.99±0.15	2.00±0.00	0.060
Before anesthesia induction	1.97±0.15	2.00±0.00	0.044
Recovery	1.84±0.37	1.77±0.42	0.108
Sedation			
Before melatonin administration	1.0±0.0	1.0±0.0	1
Before anesthesia induction	1.02±0.15	1.0±0.0	0.044
Recovery	2.06±0.54	2.34±0.52	0.049
Propofol dose (mg/kg)	49.88±14.48	77.38±23.56	0.002

Note: Data are expressed as the mean ± SD, and analyzed by independent *t*-test. Melatonin group: administered 3 mg of melatonin at 50 minutes before surgery; placebo group: administered 3 mL of distilled water at 50 minutes before surgery. Anxiety, orientation, and sedation were assessed by Visual Analogue Scale score, orientation scoring, and sedation scoring, respectively.

thetia induction ($P = 0.44$) and lower in the melatonin group before the induction. Though no significant difference was seen in orientation at the recovery time, it was higher in the melatonin group. In addition, there was no significant difference in the sedation between the two groups before melatonin administration ($P < 0.05$), before anesthesia induction ($P = 0.44$) and recovery ($P = 0.049$). A statistically significant difference was observed in propofol dose between both groups ($P = 0.002$), whereas the dose was lower in the melatonin group than the placebo group (Table 5).

DISCUSSION

The results of the double-blinded clinical trial showed that MAP was lower in the melatonin group than that in another group at all times and did not have a sudden increase in the placebo group at the time of extubation, but low in the melatonin group, while no statistically significant difference was found in

HR between both groups ($P < 0.05$), but HR was lower in the melatonin group. Based on the results, no significant difference was seen in SaO₂ ($P < 0.05$) and in EtCO₂ ($P > 0.05$) between both. Though anxiety was less in the melatonin group before anesthesia induction ($P = 0.013$) and recovery ($P = 0.034$), orientation was less in melatonin group than another before the induction ($P = 0.44$). Though no significant difference was found in orientation at recovery time, it was higher in the melatonin group whose sedation was better before anesthesia induction ($P = 0.44$) and recovery ($P = 0.049$) and whose propofol dose used was lower than the placebo group ($P = 0.002$). Here, we continue to explore some concerned studies: Anderson's results⁷ were consistent with ours, whereby anxiety and pain were less in the melatonin group. Ionescu et al.'s study²² aimed at assessing the effect of melatonin premedication in laparoscopic cholecystectomy suggested that sedation was lower in the melatonin group than that in midazolam and



that melatonin can be successfully used as a premedication in cholecystectomy surgery. Their results were consistent with ours. Isik et al.²³ conducted an interventional study to compare melatonin and midazolam premedication in child anxiety, which was done in children undergoing dental treatment, showing that placebo, like melatonin, had no effect on the anxiety. Their results were not consistent with ours. This could be due to small sample size in each group in the Isik study and while the target group was children, adults (> 15 and < 55 years) were targeted in our study.

In the study by Turkistani et al.¹⁶ addressing the effect of melatonin premedication and propofol dose for induction, 45 patients undergoing different surgeries were enrolled and randomized into three groups: The former two groups were given melatonin 3 mg and 5 mg, respectively, as a premedication at 100 minutes before surgery, while no drug was administered to the third group. Afterwards, 10 mg of propofol was given in the anesthetic process every 5 minutes to attain a BIS value of 45. Eye responses and eyelid reflexes were assessed and the total propofol dose was recorded, reporting the total dose for propofol 25 mg in the placebo group and 19.5 mg in melatonin 3 mg group and 20.9 mg in melatonin 5 mg group ($P < 0.05$). The anxiety was higher in the placebo group than that in the other groups. No significant difference was found in recovery time among all groups. Melatonin 3 mg or 5 mg is recommended to reduce propofol dose to reach the BIS value of 45.¹⁶ Their results were consistent with ours.

Naguib et al.'s study¹⁹ compared melatonin and midazolam as a premedication in adults, where 84 women received 0.5, 1, and 2 mg/kg of midazolam, melatonin, and placebo, respectively, at 100 minutes before anesthesia. Sensation, anxiety, and orientation were then recorded at 10, 30, 60 and 90 minutes after premedication, and at 15, 30, 60 and 90 minutes in the recovery room. Subjects receiving midazolam and melatonin premedication showed a significant decrease in anxiety and sedation in the placebo group. Those who received midazolam 0.2 mg/kg had an increased level of sedation at 90 minutes after surgery, in comparison with those receiving melatonin 0.05 and 0.1 mg/kg at that time. Premedication with melatonin 0.05 mg resulted in less anxiety, lower sedation, and enhanced recovery. Their results were consistent with ours.

The sedation, anxiety and propofol dose used were found to be lower in the melatonin group than in the placebo group. Melatonin 3 mg is recommended to reduce propofol dose to achieve the BIS of 40.

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Author contributions

Study conception: AN, SF, AK, LA; data collection: LA; data acquisition and analysis: HM; data interpretation: AN, AK; manuscript writing: HM. All authors approved the final version of the manuscript for publication.

Conflicts of interest

There is no conflict of interest.

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Institutional review board statement

The protocol of study was approved by the Ethical Committee of Arak University of Medical Sciences with IR.ARAKMU.REC.1395.432 code in July 2016. In addition, it was registered in Iranian Registry of Clinical Trials with IRCT20141209020258N98 in September 2016.

Declaration of patient consent

The authors certify that they have obtained patients or their legal guardians consent forms. In the form, patients or their legal guardians have given their consent for the patients' images and other clinical information to be reported in the journal. The patients or their legal guardians understand that the patients' names and initials not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Reporting statement

The writing and editing of the article was performed in accordance with the CONSolidated Standards of Reporting Trials (CONSORT) Statement.

Biostatistics statement

The statistical methods of this study were reviewed by the biostatistician of Arak University of Medical Sciences, Iran.

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Data sharing statement

The data could be shared if requested but the patients completed the informed consent.

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