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A Comparative Study of the Effect of Oral Dextromethorphan and Placebo on the Pain After Vitrectomy Surgery: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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Abstract

Background: Postoperative pain is a major complication in patients undergoing eye surgery. N-methyl-D-aspartate (NMDA) receptor antagonists are widely used to manage postoperative pains. Dextromethorphan, as an NMDA antagonist, is commonly used as an oral drug.
Objectives: This study was conducted to evaluate the effect of Dextromethorphan on post-operation pain and sedative effect in comparison to placebo.
Methods: A double-blinded, placebo-controlled, randomized clinical trial, upon 60 patients undergoing vitrectomy surgery was done. Thirty patients received 30 mg oral Dextromethorphan before the operation, and 30 patients received a placebo. Post-operation pain and sedation were evaluated after zero, one, two, and six hours.
Results: Post-operation pain was significantly lower in patients who received Dextromethorphan at zero, one, and two hours after operation ($P < 0.001$); however, not at six hours after operation ($P = 0.11$). Sedative effect was higher in the Dextromethorphan group at zero ($P = 0.03$) and one hour ($P = 0.01$) after operation.
Conclusions: Prescribing oral Dextromethorphan before a vitrectomy surgery could reduce postoperative pain. It also has postoperative sedation effects.

Keywords: Antagonists, Dextromethorphan, N-Methyl-D-Aspartate, Pain, Placebo, Postoperative, Receptors, Vitrectomy

1. Background

Vitrectomy is one of the eye surgeries and is effective in reducing vision loss. Postoperative pain is a major complication in patients undergoing eye surgery (1, 2). Postoperative pain control methods are one of the challenges of the Anesthesiologist and surgical specialist. Different methods have been introduced in this regard and acute pain services have been formed in hospitals. Each of the methods of reducing acute postoperative pain, ranging from the prescription of sedative before surgery to central and peripheral nerve blocks, has special importance (3, 4). Studies have investigated the control of postoperative pain with low-risk drugs used before surgery and reduce the need for opioids to prevent pain after surgery (4). Preemptive analgesia is one of the proper methods for controlling postoperative pain or taking the sedative drug before surgery and before the onset of surgery stress and histological damage, which has shown good results in studies (5-7). NMDA receptor antagonists are widely used to manage postoperative pains (8, 9). Dextromethorphan, as an NMDA antagonist (10), is commonly used as an oral drug. It has also been studied widely for its use as an analgesic drug (11-19). Some studies have shown the effect of dextromethorphan in reducing postoperative pain or reducing opioid use (8, 20-22), however, others have not shown this effect (23, 24). As dextromethorphan reduces the cumulative response during second pain and given the low side effects of this drug, it can be a good candidate for controlling the pain after surgery.

2. Objectives

This study was conducted to compare the effect of oral dextromethorphan and placebo in controlling acute pain after vitrectomy surgery.

3. Methods

The study was a double-blind, randomized clinical trial. The study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran, and registered at the Iranian Registry of the Clinical Trials with the registration number of IRCT2017102510599N21.

3.1. Sample Preparation

The sample size was estimated using the below formula.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left({\sigma_1}^2 + {\sigma_2}^2\right)}{\left(\mu_1 - \mu_2\right)^2} \quad (1)$$

According to previous studies (20), dextromethorphan reduced the pain score of patients with a Visual Analog Scale (VAS) by 0.9 and a standard deviation of 1.1. Considering the alpha error of 0.05 and the power of 80% for the study, the sample size was determined to be 25 people in each group; 30 people were considered for each group, which accounted to a 20% of drop out.

Convenience sampling was used. Enrolled patients were taken from all the referred patients to the Rasoul-Akram Hospital (a referral university general hospital in Tehran, Iran). Patient's informed consent was obtained. The study was done from March to November 2017.

The inclusion criteria included aged between 18 and 70 years, American Society of Anesthesiologists (ASA) class II-I, candidate for vitrectomy surgery, and were able to communicate verbally or in writing. The exclusion criteria included drug or alcohol abuse, consuming daily analgesia or 48 hours before surgery, dizziness or a frequent headache, cardiovascular or respiratory diseases, renal failure, and liver dysfunction. For making a double-blind study, the patient and the person who evaluated the outcome were not aware of the type of intervention received. Patients were randomly assigned to two groups (each containing 30 subjects) by selecting pocket 1 or pocket 2.

3.2. Interventions

As entering the operating room, the patients in the intervention group received an oral dose of 30 mg of Dextromethorphan (Alhavi Company, Iran) before anesthesia. The control group received a placebo. The anesthetic drug was the same for all patients, and it was as follows: Midazolam 0.12 mg/kg, Fentanyl 2 μg/kg, followed by Cisatracurium 0.2 mg/kg, and Nesdonal 5 m/kg. Then, they were intubated and underwent anesthesia with Propofol 100 μg/kg/min. Patients underwent standard monitoring including electrocardiogram, pulse oximetry, and blood pressure.

3.3. Measurements

The severity of postoperative pain was assessed by a VAS (0 = no pain, 10 = worse possible pain) (25), at the end of surgery, during recovery, one hour, two hours, and six hours after surgery, in the ward by a person who was not aware of the control and intervention groups. This scale has the ability to quantify and is selected based on the patient's opinion. The severity of the patient's sedation was also determined at the same intervals, according to the physician's opinion. For this variable, Ramsay sedation assessment scale (awake levels (1 - 3), asleep levels (4 - 6)) was used (26). The frequency of nausea and vomiting was evaluated and recorded. The weight and height measurements were done using a Seca balance and stadiometer to determine the Body Mass Index (BMI). Age, gender, and controlled underlying disease were also recorded for each patient. Vital signs of the patients were recorded during the mentioned periods.

3.4. Statistical Analysis

Collected data were analyzed using the SPSS Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, Ill, USA). The data were analyzed by the intention-to-treat (ITT) approach. Data normality was tested by Kolmogorov-Smirnov test. For the qualitative variables, frequency and percentage were calculated, and the Chi-square test was used for comparing them between two groups. For quantitative variables, if the distribution was normal, the mean and standard deviation was reported, and if the distribution was not normal, median was reported. Quantitative data analysis was performed using Independent *t* test (for a normal distribution) or Mann-Whitney U test. The repeated measure ANOVA was used for comparing VAS or sedation scale at recorded times in two groups. In statistical analysis, P-value < 0.05 was considered significant.

4. Results

A total of 69 patients were investigated; three patients were excluded due to being an age above 70 years, two patients were excluded due to cardiovascular diseases, one patient was excluded due to liver dysfunction, and three patients were not consent to participate in the study. Finally, information for 60 patients in two groups (n = 30) were analyzed (Figure 1).

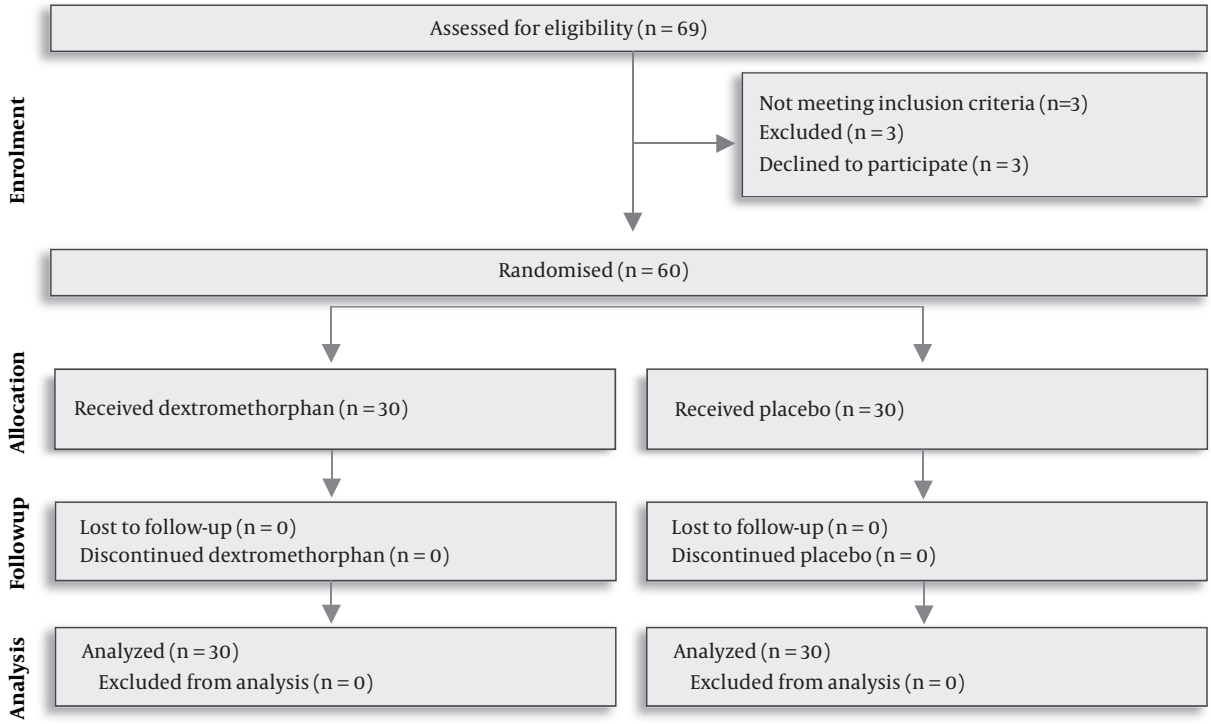

Figure 1. Flow diagram of patients in the trial. n = number of patient

The demographic data of patients in the two groups are presented in Table 1. There was no significant difference between the two groups. As shown in Table 1, the pain severity after surgery was significantly lower in the Dextromethorphan group at zero, one, and two hours than that in the placebo group ($P < 0.001$). The severity of sedation in the Dextromethorphan group at zero ($P = 0.03$) and one hour ($P = 0.01$) after surgery was significantly higher than that in the placebo group.

Comparison of pain scores and sedation scale in all states in times zero, one, two, and six hours after surgery in both groups are shown in Figures 2 and 3.

Incidence of nausea and vomiting were the same in both groups; there was no significant difference ($P = 0.15$).

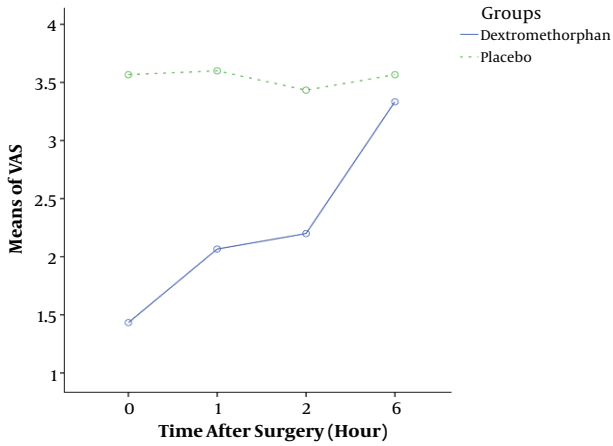

Figure 2. Comparison of VAS in dextromethorphan and placebo groups. VAS = Visual Analog Scale

5. Discussion

The current research showed that Dextromethorphan has an analgesic and sedative effect in postoperative time. Simultaneous analgesic and sedative effect of the drug make it to be an appropriate candidate for using it in patients. It is likely that Dextromethorphan is suitable for patients with such conditions. Another finding of the current research suggests that the analgesic and sedative effects of Dextromethorphan were remained up to two hours after the surgery and did not differ significantly in the next few hours. The practical use of this finding is that dextromethorphan can be used in cases where the surgery has limited pain, and the patient needs to prevent the pain for

Table 1. Demographic Data, Visual Analog Scale and Sedation Scale in Terms of Two Groups

Variable	Placebo (n = 30)	Dextromethorphan (n = 30)	P Value
Age[a], y	56.6 ± 3.9	57.5 ± 4.7	0.4
Gender (female / male)	14 / 16	15 / 15	0.8
BMI[b], kg/m^2	25 (24 - 26.25)	24 (24 - 25)	0.4
Number of patient with controlled underlying disease	23	24	0.75
Visual Analog Scale[b]			
Recovery (0)	4 (3 - 4)	1 (1 - 2)	< 0.001
1 hour after operation	4 (3 - 4)	2 (2 - 2)	< 0.001
2 hours after operation	4 (3 - 4)	2 (2 - 2.25)	< 0.001
6 hours after operation	4 (3 - 4)	3 (3 - 4)	0.11
Sedation scale[b]			
Recovery (0)	1(1 - 2)	2 (1 - 2.25)	0.03
1 hour after operation	1 (1 - 2)	2 (1 - 2)	0.01
2 hours after operation	2 (1 - 2)	2 (1 - 3)	0.16
6 hours after operation	1.5 (1 - 2)	2 (1 - 2)	0.1
Number of patient who had side effect			
Incidence of nausea-vomiting	0	2	0.15

[a] Values are expressed as mean ± SD.
[b] Values are expressed as median (25th - 75th percentiles).

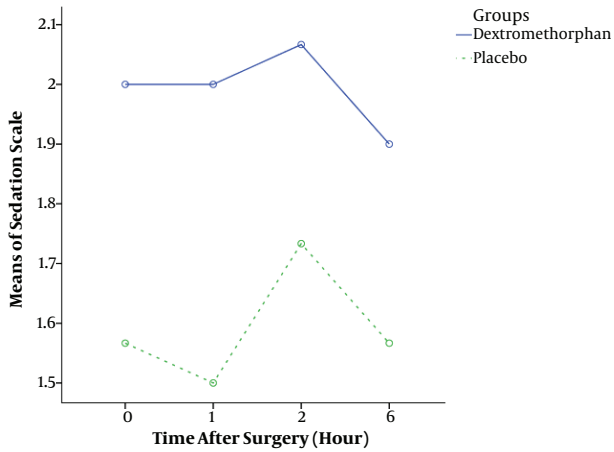

Figure 3. Comparison of sedation scale in dextromethorphan and placebo groups

a short time. The findings of the current study were similar to Entezary et al. (20), Suski et al. (27), Wu et al. (18) and several other studies (28-31).

Entezary et al.'s study showed oral Dextromethorphan reduced postoperative pain in patients with knee arthroscopy (20). Suski et al. studied the analgesic effect of Dextromethorphan on postoperative pain in adolescents with idiopathic scoliosis. This study reported that the addition of Dextromethorphan to morphine could reduce pain only in the early postoperative period (27). Wu et al., in one study, reported the effect of Dextromethorphan combined with Lidocaine on pain relief after laparoscopic cholecystectomy (18). Weinbroum et al. examined the effect of Dextromethorphan on pain of patients undergoing surgical bone malignancies. In this study, the patients received placebo or Dextromethorphan 90 mg before and two days after surgery. It was found that people who received Dextromethorphan experienced 50% less pain than the other group for more than two days after surgery. Additionally, they reported postoperative sedative effects less by 40% - 60% and reported the side effects less by 50% (30). Rafiei et al. examined the effect of dextromethorphan on patients undergoing tonsillectomy and concluded that taking dextromethorphan can reduce the postoperative pain (32).

McCartney et al. in a qualitative systematic review, evaluated the effect of dextromethorphan on reducing postoperative pain beyond the clinical duration of action of the drug and reported significant immediate and preventive analgesic benefit in 67% of studies (29).

Inconsistent with our study, some studies did not show the significant effect of Dextromethorphan on postoperative pain (11, 13, 23, 24, 33). Abu-Samra and Ismaeil (11) and Aoki et al. (13) showed that in their studies premedication oral Dextromethorphan prior to nasal (11) and oral (13)

surgery decreased postoperative pain, however, this was insignificant in comparison with the placebo group.

Amani and Madineh investigated the effect of Dextromethorphan on children undergoing adenotonsillectomy surgery. There was no significant difference between the groups who received dextromethorphan and the placebo group in terms of severity of pain (33).

The current research was conducted on patients with a similar type of surgery. Using an affordable and inexpensive drug was one of the strengths of our study. Our limitation was adherence to Non Per Oral (NPO) time before surgery.

The length of the surgery undoubtedly influences the use of Dexamethasone before the operation and observing its anti-anxiety effect, and it is proposed to be considered in next studies, and in addition to the initial dose, the next doses would be considered.

5.1. Conclusion

Prescribing 30 mg Dextromethorphan before surgery can reduce postoperative pain in patients with vitrectomy; it also has postoperative sedation effects.

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Footnotes

Authors' Contribution: Study concept and design: Seyed Hamid Reza Faiz, Poupak Rahimzadeh; acquisition of data: Nasim Nikoubakht; analysis and interpretation of data: Seyed Hamid Reza Faiz; drafting of the manuscript: Seyed Hamid Reza Faiz, Poupak Rahimzadeh, Nasim Nikoubakht, Azadeh Sayarifard; critical revision of the manuscript for important intellectual content: Seyed Hamid Reza Faiz, Poupak Rahimzadeh, Nasim Nikoubakht, Azadeh Sayarifard; statistical analysis: Azadeh Sayarifard; administrative, technical, and material support: Nasim Nikoubakht, Poupak Rahimzadeh; study supervision: Seyed Hamid Reza Faiz, Poupak Rahimzadeh.

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