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Comparison of the use of remifentanil in infusion and patient-controlled methods for sedation purposes

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ABSTRACT

Aims: In this study, remifentanil infusion and patient-controlled bolus use with a patient-controlled analgesia (PCA) device were compared in terms of sedation in patients who underwent spermatic vein ligation under local anesthesia.

Methods: Thirty patient between the ages of 15-45 who were in the ASA I-II group were included in the study. They were randomly divided into 3 groups using the closed envelope method; continuous infusion (Group I), patient-controlled sedation (Group P) and control group (Group C). All patients were premedicated with intravenous (IV) 0.07 mg/kg midazolam. Group I was given 0.1 µg/kg/min remifentanil, Group P was given a patient-controlled 0.5 µg/kg bolus remifentanil via PCA, Group I and Group C were given physiological saline via PCA device. We hypothesized that patient-controlled bolus use would result in less drug consumption than infusion. Primary outcome; was determined as the amount of drug consumption. Secondary outcome; Intraoperative and postoperative side effects and sedation levels. In addition, hemodynamic parameters, anxiety scores, number of PCA applications and patient satisfaction were also recorded. During the operation, 2-3 L/min oxygen was administered via mask to patients whose SpO2 fell below 93%.

Results: Respiratory depression was more common in Group I, but the respiratory rate did not fall below 8 in any group. Intraoperative oxygen was required in 7 patients in Group I and 4 patients in Group P. The total amount of drug consumed was 64.4 µg in Group P and 147.5 µg in Group I. Although there was no difference in the number of PCA requests, 4 patients in Group I, 2 patients in Group P, and 1 patient in Group C never pressed the device. In terms of patient satisfaction, 30% of patients in Group I said it was excellent, while patients in Group C said it was not excellent. The number of patients who evaluated the method as excellent and very good was higher in Group P than in Group I.

Conclusion: Patient-controlled bolus administration of remifentanil provided superior primary outcome with significantly less drug consumption. Secondary outcome were similar. Patient-controlled bolus administration with respiratory monitoring can be used safely.

Keywords: Local anesthesia, patient-controlled sedation, remifentanil, spermatic vein ligation

* This study was presented as an oral presentation at the 7th Balkan Anesthesia Days (30 April - 02 May, 2021).

INTRODUCTION

Spermatic vein ligation can be performed under general, spinal or local anesthesia (LA). The choice of anesthesia technique depends on various factors such as suitability of the procedure for the patient, surgeon's choice, patient acceptance, safety, perioperative pain control, time to return to normal activity, need for monitoring and cost effectiveness. Compared to general anesthesia, local anesthesia has less pain, postoperative analgesic requirement, postoperative nausea and vomiting, and is associated with shorter anesthesia and hospital stay.[1] However, preoperative and intraoperative anxiety is common in all patients undergoing LA. For this reason, sedation is needed in local and regional anesthesia.[2] An ideal sedative agent should have a rapid onset of action, allow control of the duration and level of sedation, and provide rapid recovery and uncomplicated discharge.[3,4] The drugs used may cause significant respiratory depression or delayed recovery in increasing doses. It has been shown that continuous IV infusions of anesthetic and analgesic drugs provide fewer intraoperative side effects, less cardiorespiratory depression and shorter recovery time.[5,6]

Intermittent bolus doses of drugs may cause temporary respiratory and circulatory depression, the patient does not lose cooperation in conscious sedation without suppressing protective reflexes, Complies with commands. As the sedation level increases, loss of cooperation, confusion and hypoxemia may occur.[7]

The primary aim of Monitored Anesthesia Care (MAC) recommended by ASA is the patient's comfort and safety during surgery. It involves the administration of IV drugs to provide sedation, anxiolysis, amnesia and analgesia in minor diagnostic, therapeutic and local-regional anesthetic procedures. Monitoring is the same as that required for general anesthesia (ECG, non-invasive blood pressure measurement, peripheral oxygen saturation and end-tidal CO2 monitoring).[5]

In order to obtain suitable conditions for the anesthetist and surgeon as well as the patient during the operation, IV sedative-hypnotic and analgesic drugs are frequently used as intermittent bolus or infusion. Infusion is administered in two ways: doctor- controlled or patient-controlled.[8]

Patient-controlled sedation (PCS) method using the PCA device, where the patient participates in the treatment, has now also entered practice. It has been shown that the general condition and expectations of patients who participate in treatment with this method are positively affected.[9]

In this study, we compared the short-acting μ-receptor agonist remifentanil with placebo using continuous IV infusion and PCS methods for sedation after midazolam premedication in patients who will undergo spermatic vein ligation under local anesthesia. We aimed to evaluate the amount of medication used, side effects, sedation levels, anxiety scores and patients' satisfaction with the method. In this study, superior primary outcome were obtained and less drug consumption was observed with patient-controlled bolus administration of remifentanil in patients who underwent spermatic vein ligation under local anesthesia. As a secondary outcome, it was observed that intraoperative and postoperative side effects were less and sedation levels were similar with patient-controlled bolus use of remifentanil. With respiratory monitoring, 0.5 μg/kg bolus remifentanil could be administered safely via PCA device.

METHODS

The study was conducted in 2001 as an anesthesiology and reanimation specialty thesis. This study was initiated after institutional approval was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In this study, 30 patient from the American Society of Anesthesiologist (ASA) physical status I-II group, aged between 15 and 45, who would undergo spermatic vein ligation under local.

Urology Clinic, were included in the study with their informed consent. Patients with any neurological disorder, renal or hepatic failure, a history of benzodiazepine and opioid use, anesthetic drug intolerance and cooperation difficulties were not included in the study. In patients whose oral intake had been restricted for at least 6 hours in advance, an IV line was opened with a 22G on the back of the hand and physiological saline infusion was started. The PCA device was introduced to the patients and they were told to press the button of the device when needed during the operation.

All cases were given 0.07 mg/kg IV midazolam for premedication. They were random divided into 3 groups according to sedation techniques: continuous infusion (Group I), patient-controlled sedation (Group P) and control group (Group C). All patients were administered local anesthesia with 2% prilocaine hydrochloride by the surgeon. Group I was given 0.1 μg/kg/min remifentanil infusion with a simple syringe-infusion pump system (Pilot A2- Fresenius vial) and saline solution with a locked period of 5 minutes with a PCA (Acute pain manager apm abbott) device. Group P was given remifentanil (ULTIVA TM glaxo wellcome) via PCA at a bolus dose of 0.5 μg/kg. Group C received only PCA and physiological saline. In order to ensure accurate evaluation of the number of requests, physiological saline was administered to the subjects in the control and infusion groups via the PCA device. The patients' heart rate (HR), mean arterial pressure (MAP), SpO2 and respiratory rates were recorded before sedation and every 5 minutes throughout the procedure. Intraoperative and postoperative side effects of remifentanil (MAP <60 mmHg, pulse <60, bradypnea <8, desaturation <93%, nausea, vomiting, itching, tremor, arrhythmia) were examined. At the end of the procedure, the operation time and the total remifentanil doses used were recorded. Anxiety was evaluated with VAS (0 mm-none, 100 mm-very present). Mini mental test was applied to evaluate orientation and adaptation. In this test, which consists of a total of 30 points, a score of 24 or below was considered an indicator of serious cognitive dysfunction.[10]

Cooperation was evaluated with a 5-score test.[11] Sedation level was evaluated with Ramsey sedation score. Two-three points were considered sufficient for conscious sedation.[12] A picture card test was performed intraoperatively to evaluate amnesia.[13] At the end of the operation and 2 hours later, their failure to remember the previously shown picture cards was considered as anterograde amnesia. Patient satisfaction was evaluated with a 5-point verbal scale 2 hours postoperatively (1 excellent, 2 very nice, 3 nice, 4 not bad, 5 bad).[14]

The total button pressing frequency of the subjects during sedation was recorded from the memory information of the device. At the end of the 2nd and 24th postoperative hour, the patients were questioned about their complaints of nausea, vomiting and pain.

Statistical Analysis

'SPSS for Windows version 9.01' program was used for statistical evaluation. Kruskal wallis ANOVA and median test were used where necessary. mann-whitney U test was used to find different groups. chi-square test was used to compare side effects grouped as present or absent. The significance level was accepted as $p<0.05$.

RESULTS

There was no difference between the groups in terms of age, body weight and operation times ($p>0.05$) (Table 1). There was no difference in MAP values between the three

groups. Hypotension and bradycardia were not observed in any case (p>0.05). There was no statistical difference in HR values within and between groups.Desaturation was considered when peripheral O_2 saturation fell below 93%. O_2 was administered continuously to 7 patients in the infusion group, and to 4 patients in the PCS group intermittently via a mask at a rate of 2-3 L/min. Respiratory depression was observed in fewer cases in the PCS group.

Table 1. Demographic data and operation times (Med ± SD)

	Grup I	Grup P	Grup C
Age (year)	25.1±5.46	30.6±8.74	26.5±6.51
Weight (kg)	76.8±9.56	81.2±12.7	69.0 ±15.93
Operation time (min)	27.3±6.11	28.0±6.74	23.3 ± 7.07

Min: Minumum, SD: Standard Devision

As seen in Figure 1 (p<0.01), respiratory rate showed a significant difference in Group I (p<0.05). However, it never fell below the hypoventilation limit of.[8]

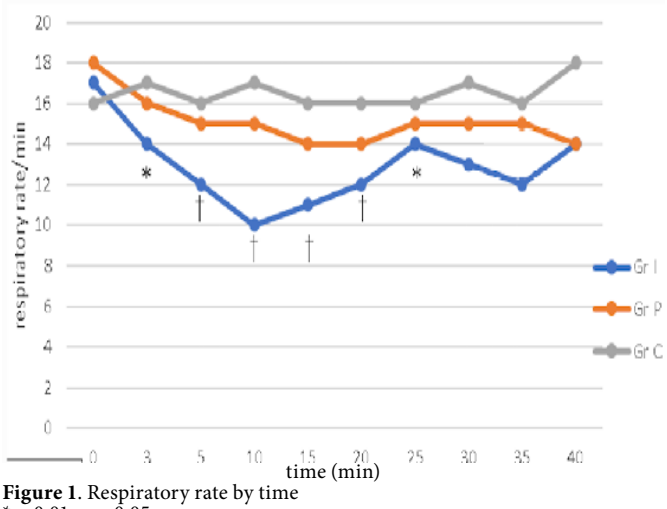

Figure 1. Respiratory rate by time
*p<0.01, +p<0.05

While preoperative and postoperative anxiety levels did not differ between the groups, the postoperative anxiety levels of the patients in all three groups were significantly lower than before surgery (P<0.001) (Table 2).

Table 2. Preoperative and postoperative anxiety levels

	Grup I	Grup P	Grup C
Preoperative anxiety	43.7± 5.19.7	48.5± 28.2	46.8± 31.3
Postoperative anxiety	0.0 ± 0.0*	0.5 ± 0.5*	5.0 ± 12.6*

* p < 0.001

According to the mini-mental test results, which evaluate mental status and orientation, postoperative values were lower than before surgery, but this was not statistically significant (p>0.05). There was no difference between the groups in amnesia evaluation (p>0.05).

Patients who were awake and cooperative throughout the operation did not remember how many times they pressed the PCA button.The total amount of drug consumption was statistically significantly different between the two groups receiving remifentanil. In Group P, it was 147.5±48.37 and 64.4±40.95 (p<0.001) (Figure 2). All patients evaluated with the 5-point cooperation test were cooperative throughout the operation.[4-5] There was no statistical difference between the groups.Sedation scores are shown in Figure 3. Level 2-3 was considered sufficient for conscious sedation. In group I, the deepest sedation was seen in the 20th-30th minutes with a value of 3.5, while in group P the deepest sedation was seen in the 10th-20th minutes with a value of 3. In the Group C the sedation score was always 2. The scores at the 5th, 10t^{h}, 20th and 30th minutes in Group I and the scores at the 10th and 20th minutes in Group P were significantly different compared to Group C (p<0.05). Patients who were cooperative and alert even at the deepest levels of sedation responded fully to verbal stimulation.

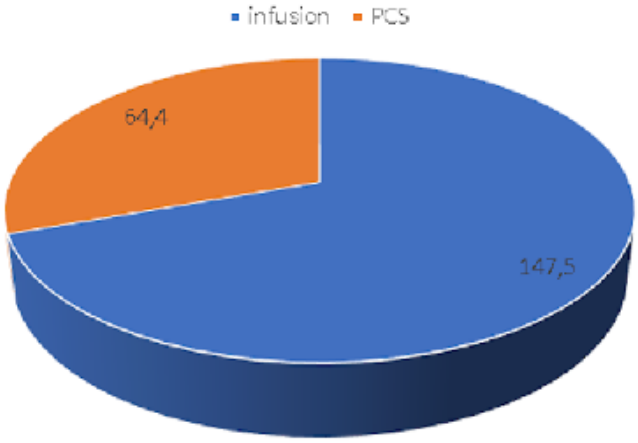

Figure 2. Remifentanil consumption amount(ug)

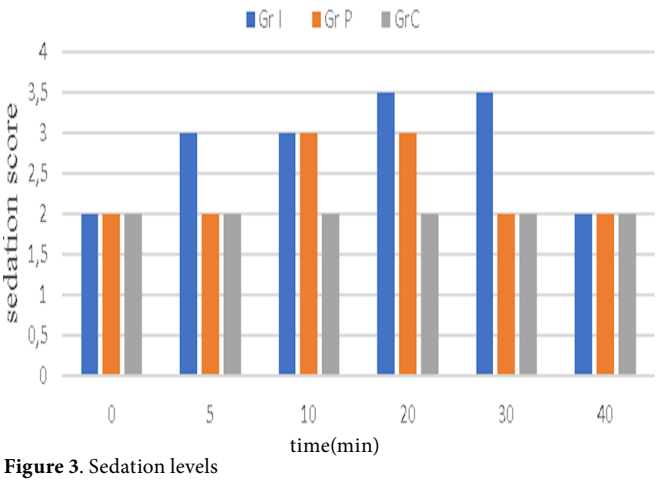

Figure 3. Sedation levels

Patient satisfaction; It can be seen in Table 3. No statistical difference was found between the groups (p>0.05). While 30% of the patients in Group I evaluated the method as excellent, it was not evaluated as excellent in the control group that did not receive remifentanil. The number of patients who evaluated the method as excellent and very good was higher in Group P than Group I. No negative comments were made regarding the method used in any group. In the perioperative period, pain was observed in 2 patients in the infusion and PCS group and in 4 patients in the control group (p>0.05). During this period, the rate of PCA use increased. In this situation, additional local anesthetic was administered.

Table 3. Patients' satisfaction

	Grup I	Grup P	Grup C
Excellent	3	1	-
Very good	2	5	4
Good	5	4	5
Not bad	-	-	1
Bad	-	-	-

The amount of local anesthetic used was similar in all groups. The numbers of medication request are shown in Table 4. It was similar in Group P and Group C, but less in Group I. It was not significant (p>0.05). Four patient in Group I, 2 patients in Group P and 1 patient in Group C had never pressed the PCA device.

Table 4. PCA Request count

	Grup I	Grup P	Grup C
Successful demands	9	14	14
Failed demands	5	8	9
Total demands	14	22	23
No demand(n)	4	2	1

Among the side effects of remifentanil, itching, bradycardia, hypotension, rigidity, tremor and arrhythmia were not observed in any patient. Nausea was observed in 2 patients in Group I, one in the postoperative 10th minute and the other in the postoperative 30th minute and 2nd hour. There was no vomiting. No nausea or vomiting was observed in Group P. In the control group that did not receive remifentanil, orthostatic hypotension and vomiting were observed in one patient in the 2nd postoperative hour (p>0.05).There were no complaints of pain, nausea or vomiting in the patients contacted by phone at the 24th postoperative hour.

DISCUSSION

In general, stress is a very important factor in all surgical interventions. Even if patients do not feel any pain under local or regional anesthesia, the discomfort caused by stress affects both the patient and the surgical team. To control perioperative anxiety, sedative agents are usually given as IV boluses under the supervision of the anesthesiologist. In PCS, the patient self-administers the medication in small doses as needed. It is a great pleasure for the patient to be able to control his anxiety. Sedative agents that have a rapid onset of action, a short half-life, no active metabolites, and a rapid and trouble-free recovery are ideal for PCS use. While the selected agent, locking conditions and bolus amounts primarily affect PCS settings, the patient's psychological state, intellectual level and informing about the procedure are other effective factors.

Research has shown that patients are better aware of their discomfort, pain, and the sedation they need during interventions than an anesthesiologist or nurse. The idea that patients can best respond to their own needs creates positive emotions in the patient. It has been noted that these feelings caused by PCS in patients are due to the following three factors. The first is that the worry of someone giving too much medication is eliminated, the second is that the patient is free from dependence on someone, and the third is that it is possible to receive immediate treatment.[9] Benzodiazepines are generally used in this method. While patient-controlled IV therapy was previously used only for analgesia, the foundations of PCS were first laid in 1989 when Galleti et al used diazepam for anxiolysis in a group of 50 people.[15] PCS has also been successfully applied to elderly and pediatric patients.[16,17] The success of PCS depends on the sedative agent chosen, the level of sedation provided, and the patient.[18] In addition to postoperative pain control, PCA devices are also used in sickle cell anemia crisis, gynecology, intensive care units and intraoperatively.[19,20]

Although patient satisfaction in PCS applications is better than other sedation methods, the expensiveness of PCA devices causes additional costs such as the need for a special set for each patient, which creates limitations and disadvantages in practice.[21] Benzodiazepines are drugs commonly used for anxiolysis, amnesia and sedation. Midazolam has a rapid onset of action, a short elimination half-life (1-4 hours) and good recovery properties. In addition to its hypnotic and anticonvulsant effects, it causes anterograde amnesia.[22]

Although there are studies showing that the use of remifentanil alone is sufficient to provide sedation, it has been reported that it should be given with 2 mg IV midazolam at a dose of 0.05-0.1 μg/kg/min to provide amnesia and analgesia.[6] In another study, clinically significant respiratory depression was detected after a bolus dose of remifentanil in patients premedicated with midazolam.[23] Additionally, it was observed that respiratory depression occurred in direct proportion to the increase in the midazolam dose in the combination of remifentanil and midazolam. Gold et al.[25] also used remifentanil alone and in combination with midazolam during outpatient surgery for MAC. They reported that low-dose (0.05 μg/kg/min) remifentanil combined with midazolam (2 mg) caused slightly more sedation, less anxiety and side effects.[24] A 0.07 mg/kg sedation dose of midazolam has been recommended, but it has been reported that it may reduce protective reflexes if opioids are used before treatment.

In ESWL, it has been stated that in addition to the lower infusion dose of remifentanil with the PCS method, the 10mcg bolus dose is more effective and causes fewer side effects.[26] In some studies, dose adjustments were made to reach the desired level of sedation in continuous infusion.[11] In our study, the rate was kept constant in the infusion group. Based on previous studies, we preferred the 0.1 μg/kg/min infusion dose and 0.5 μg/kg bolus dose as we found them reliable throughout the surgery. We provided adequate sedation and did not encounter excessive sedation in any patient.

PCS is also recommended to avoid unnecessary deep sedation during ERCP.[21] Remifentanil, used at a dose of 0.1-0.5μg/kg/min in awake fiberoptic intubation, increased tolerance by providing significant analgesia and suppressing the cough reflex. Although recovery from remifentanil is very rapid, it can be reversed with naloxone if necessary.[27] It has been reported that 0.05-0.15 μg/kg/min remifentanil infusion may be an alternative to 25-75 μg/kg/min propofol infusion in ambulatory operations performed under LA. In the same study, it was clearly shown that drug infusion rates generally need to be changed after 15-20 minutes and that active site

concentrations of drugs continue to increase during the early infusion period.[23]

Remifentanil was used together with the PCA device for analgesia and sedation in 3 pregnant women who could not have an epidural due to thrombocytopenia, and it was found to be well tolerated. Oxygen was not required at a bolus dose of 0.5 μg/kg. There was a slowdown in fetal heartbeat, but it recovered 10 minutes after the device was turned off. Remifentanil consumption (426-1050 μg/h) was observed to be strikingly variable. In this publication, in which the use of remifentanil along with PCA at birth was reported for the first time, the use of artificial respiration and naloxone was not required. PCA effectiveness is related to the size of the bolus. When the dose is low, distrust of the method may occur, and when it is high, unwanted side effects may occur.[28]

A bolus dose of 0.5 μg/kg, which was tolerated without oxygen, was also found to be appropriate in our study (20- 47.5 μg bolus dose). The doses of remifentanil required for sedation are close to the doses that cause respiratory depression. Remifentanil side effects are similar to other μ-opioid receptor agonists. Studies have shown that remifentanil reduces tidal volume and respiratory rate. However, unlike other opioids, it does not have an accumulating effect and has a short half-life, so the condition can improve within a few minutes.[6] In our study, we encountered desaturation (SpO2<93%) in two groups receiving remifentanil, more in the infusion group, but there was no significant difference between the groups.The decrease in respiratory rate seen in Group I was never below 8, but the difference between the groups was statistically significant.

Sa'Rego et al.[29] compared intermittent bolus doses of remifentanil (25 μg) and continuously variable dose infusion (0.025-0.15μg/kg/min) in addition to the use of midazolam (2 mg) and propofol (50 μg/kg/min) under MAC in ESWL. Although patient comfort is better when using remifentanil by infusion, the incidence of desaturation is higher. Although more medication was used in the infusion group, a lower pain score was found in the low dose infusion+bolus (0.05 μg/kg/min+12.5 μg) and bolus only group. Compared to infusion, it has been observed that the risk of hypoventilation does not increase and rapid recovery is achieved with bolus doses, which are found to be simple, reliable and effective, and it has been reported that dose titration should be done very carefully because it reduces tidal volume and respiratory rate.[6] In our study, respiratory depression was also seen in the infusion group, and bolus administration did not occur.

In contrast to the use of infusion in general anesthesia, it has been observed that the response to temporary noxious stimuli is better prevented by intermittent bolus application in MAC.[24] Studies have reported that it causes nausea and vomiting during remifentanil administration or in the early postoperative period.[6] In our study, we observed nausea in the infusion group, although it was not statistically significant. In the control group, one patient experienced orthostatic hypotension and vomiting at the 2nd postoperative hour.

In the studies conducted, when 0.1 μg/kg/min remifentanil infusion combined with 2, 4 or 8 mg midazolam was compared, the respiratory rate decreased more in the group combined with high dose midazolam, but intraoperative itching and postoperative nausea were observed in the deep sedation (4-5) group. Side effects such as vomiting were less common in the light sedation group.[6] PCS has been recommended for patients undergoing ERCP to avoid unnecessary deep sedation.[21] In our study, there was no difference in amnesia between the 3 groups. It has been shown in the literature that patients taking remifentanil alone fully remember intraoperative events, the degree of amnesia depends on the dose of midazolam administered, and recovery from remifentanil is rapid.[6] In our study, all cases transferred themselves from the operating table to the stretcher at the end of the operation. In Group I, stopping the infusion (while skin stitching begins) before the end of the procedure may also have an effect. Early postoperative pain is expected after remifentanil, but the 1.5-2 hour effect of local anesthetic infiltration ensures the continuation of the analgesic effect after of surgery. Our patients did not need analgesics before 2 hours. There are positive publications regarding the use of PCS in otorhinolaryngology and breast surgery performed under local anesthesia and in labor analgesia.[20,30,31]

In women using the PCA device, the duration of active labor was shorter compared to epidural, the rate of spontaneous birth was higher, and side effects were less.[32] The deeper level of sedation in the infusion group may have resulted in fewer PCA requests. The number of requests in Group C was similar to Group P, but patient satisfaction and sedation level were better in Group P. The study has limitations. Since it was a single-center study and the number of patients was small, it may not be appropriate to generalize these results to the general population.

CONCLUSION

In this study, adequate sedation was achieved with a lower dose of remifentanil using the PCS method compared to infusion. Intraoperative pain was less in the group receiving remifentanil than in the control group, and side effects were less in the PCS group than in the infusion group. We concluded that PCS can be used safely with a bolus remifentanil dose of 0.5 μg/kg under respiratory monitoring in cases undergoing surgery under local anesthesia.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted in 2001 as an anesthesiology and reanimation specialty thesis. This study was initiated after institutional approval was obtained.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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