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ORIGINAL RESEARCH

Better Treatment Values in Local Application of Tranexamic Acid (TXA) than Intravenous Application with the Same Dose in Total Hip Arthroplasty

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ABSTRACT

Introduction: The aim of our study was to investigate the hemostatic effect of local and intravenously administered tranexamic acid (TXA) at the same dose in total hip arthroplasty.
Methods: The prospective study included 72 patients who underwent total hip arthroplasty in our hospital between March 2018 and March 2019. The patients enrolled in the study were randomly divided into two groups: the observation group (36 patients were injected with 2.0 g TXA in 10 mL 0.9% NaCl using the joint cavity drainage tube after suturing the joint capsule) and the control group (36 patients were given an intravenous infusion of 2 g TXA in 200 mL 0.9% NaCl 30 min before the operation). In each patient, apparent blood loss, hidden blood loss, average blood transfusion, and the number of cases receiving blood transfusion were compared between the two groups after treatment. Hematocrit (Hct) and hemoglobin (Hb) levels were recorded at postoperative day (POD) 1, 2, 3, 7, and 10. We also recorded the levels of C-reactive protein (CRP) and interleukin-6 (IL-6) before the operation and 12 h postoperative and POD 1, 3, 7, and 10. The incidence of deep venous thrombosis and pulmonary embolism was also taken into account.
Results: In the observation group, apparent blood loss, hidden blood loss, average blood transfusion volume, and the number of patients receiving blood transfusion were lower compared than the control group ($P < 0.001$). The levels of Hct and Hb were compared between the two groups at POD 1, 2, 3, 7, and 10, and the observation group reported higher levels of Hct and Hb ($P < 0.001$). The levels of CRP and IL-6 were compared between the two groups at POD 1, 3, 7, and 10, and the observation group reported lower levels of CRP and IL-6 than the control group ($P < 0.001$). On POD 7, there was no pulmonary embolism in both groups, and no significant difference was observed in the incidence of deep venous thrombosis between the two groups ($P > 0.05$).
Conclusions: Local and intravenous applications of TXA at the same dose are effective approaches in terms of reducing bleeding and inflammatory reaction with a good safety profile; however, the effect of local application had superior therapeutic values.

Keywords: Hemostatic effect; Intravenous application; Local application; Total hip arthroplasty; Tranexamic acid

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Key Summary Points

Why carry out the study?

TXA has been widely used in operations with beneficial hemostatic effect

This study aimed to identify the hemostatic effect of local and intravenous applications of TXA

What was learned from the study?

Local application TXA achieved superior clinical results compared with intravenous application

INTRODUCTION

Total hip arthroplasty is regarded as an effective method for clinical orthopedic treatment of hip joint diseases such as aseptic osteonecrosis of the femoral head and ankylosis of the hip [1, 2]. It can effectively relieve pain and restore the mobility of the hip joint. However, it is believed in clinical practice that this procedure can cause significant blood loss and a high blood transfusion rate during the perioperative period of total hip arthroplasty. Given that the disease occurred mainly among middle-aged and elderly patients accompanied by subcutaneous bruising, which can result in increased infection rate after the operation, it is not conducive to rehabilitation and affects the quality of life of patients [3].

Hemostatic drugs can reduce the volume of perioperative bleeding, but easily leads to deep venous thrombosis followed by pulmonary embolism or cerebral infarction, and even death in severe cases [4]. Although intraoperative blood transfusion can supplement the blood volume of the body, it may be accompanied by a series of complications after a blood transfusion and the limited storage of domestic blood bank makes the situation even worse. Therefore, our study focused on the improvement of intraoperative hemostatic effect without increasing the risk of deep venous thrombosis. Tranexamic acid (TXA), also known as clotting acid, can be efficiently bound by plasmin and fibrin binding sites on plasminogen, which is able to inhibit fibrin degradation to achieve the hemostatic effect [5, 6].

Currently, it has been widely used in urology, gynecology, and other operations with beneficial hemostatic effect. Pan et al. [7] suggests that the application of TXA in total hip arthroplasty can effectively reduce perioperative bleeding, but other scholars reveal their concern in terms of the increased risk of deep venous thrombosis with intravenous injection [8]. Hence, the present study sought to identify the hemostatic effect of local and intravenous applications of TXA at the same dose in total hip arthroplasty and its effect on the incidence of deep venous thrombosis.

METHODS

Patients

These included 72 patients who underwent total hip arthroplasty in the orthopedic surgery department of our hospital between March 2018 and March 2019. Examples of preoperative and postoperative X-ray films are shown in Fig. 1. The patients enrolled in our study were randomly divided into the observation group ($n = 36$) and control group ($n = 36$) by the envelope method. In the observation group, there were 16 men and 20 women, aged 49 to 79, with an average age of 67.98 ± 8.87 years. In the control group, there were 15 men and 21 women, aged 48 to 78, with an average age of 66.98 ± 9.01 years. There were no significant differences in age and other general information between the two groups ($P > 0.05$). This study was approved by the ethics committee of Beijing Chao-Yang Hospital, and informed consent forms were signed by patients. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

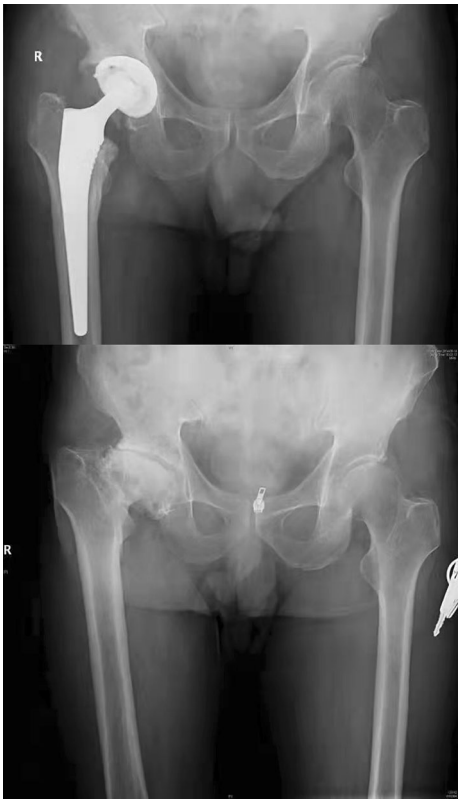

Fig. 1 X-ray films of the hip joint before and after the operation

Selection Criteria

All patients had aseptic necrosis of the femoral head, hip fracture, rheumatoid arthritis, or osteoarthritis requiring total hip replacement, and (1) all patients met the surgical indications for total hip arthroplasty; (2) all patients underwent primary unilateral hip replacement for the first time; (3) patients had complete clinical data. Exclusion criteria were as follows: (1) patients were allergic to the study drugs; (2) patients received preoperative anticoagulant, hemoglobin (< 90 g/L), platelet (< 150 × 10 g/L); (3) patients underwent bilateral total hip arthroplasty; (4) patients received revision reoperation after total hip arthroplasty; (5) patients had diabetes, cerebral infarction, pulmonary embolism (PE), malignant tumor, infectious diseases, and peripheral neurovascular diseases; (6) there was a history of vascular embolism or affected limb infection; (7) there were comorbidities (hemorrhagic hematopathy and coagulation dysfunction).

Methods

Administration

In the observation group, 2.0 g TXA was dissolved in 10 mL normal saline, which was injected in patients from the articular cavity drainage tube after joint capsule suture. In the control group, intravenous infusion of 2 g TXA in 100 mL normal saline was given 30 min before the operation.

Surgical Methods

All patients received general anesthesia, and posterolateral incision to separate the fascia. The muscles were dissected layer by layer to expose the hip joint and perform femoral neck sawing. We fitted the patient with a suitable artificial total hip prosthesis produced by LINK Co. (non-cement fixed type). The articular cavity was sutured and the severed muscles were repaired; a drainage tube was placed, the muscles were sutured layer by layer, and the drainage tube was closed 2 h after the operation.

Postoperative Management

In order to prevent thrombosis, low molecular weight heparin sodium was subcutaneously injected 6 h after the operation, once a day until patients left the hospital. The drainage tube was removed 24 h later, and muscle isometric and isotonic contractions were demonstrated when the affected limb was sensed by patients. According to the specific conditions of the patients, they could exercise properly with walkers within 3 to 5 days after the operation, and on postoperative day (POD) 2, and blood routine examination was performed. When patients appeared pale, experienced dizziness and palpitation, along with hemoglobin (Hb) < 70 g or Hb 70 g ≤ Hb < 100 g/L, allogeneic blood was injected until hemoglobin was corrected to more than 110 g/L in women or to more than 120 g/L in men. After discharge, 10 mg/day rivaroxaban was given orally for 10 days.

Research Indicators

Apparent blood loss, hidden blood loss, average blood transfusion, and the number of patients receiving blood transfusion were compared between the two groups after treatment. We monitored hematocrit (Hct) and Hb at POD 1, 2, 3, 7, and 10. In addition, the levels of C-reactive protein (CRP) and interleukin-6 (IL-6) in inflammatory indexes before the operation, 12 h postoperatively, and POD 1, 3, 7, and 10 were recorded. Lastly, the incidence of deep venous thrombosis and pulmonary embolism was recorded.

Apparent Blood Loss

Apparent blood loss = intraoperative blood loss (intraoperative blood in soaking gauze + blood volume in negative pressure drainage jar) + total postoperative drainage volume.

Hidden Blood Loss

Hidden blood loss = (preoperative Hb value − postoperative Hb lowest value) − (apparent blood loss + autologous blood transfusion + allogeneic blood transfusion). The 10 g/L hemoglobin was considered equal to 400 mL hemorrhage.

Average Volume of Blood Transfusion

Patients receiving blood transfusion were recorded in the two groups.

Incidence of Deep Venous Thrombosis and Pulmonary Embolism

On POD 7, color Doppler ultrasound was used to observe the occurrence of thrombosis and pulmonary embolism in the veins of the lower extremities.

Statistical Analysis

All the data in this study were analyzed by SPSS 18.0 software. Measurement data were expressed as mean ± standard deviation (SD), and the differences between two groups were examined by Student's *t* test. Categorical data were represented by the number of cases and percentage, and their comparison between two groups was performed by chi-squared test. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Comparison of General Data in Two Groups

First, we evaluated the general information of the two groups. We found that there was no significant difference in age, body mass index (BMI), American Society Of Anesthesiologists (ASA) score 3 or 4, Hospital for Special Surgery (HSS) score, sex ratio, surgery time, and cut length between the two groups (Table 1).

Local Application Had Lower Apparent Blood Loss, Hidden Blood Loss, and Average Blood Transfusion than Intravenous Application

The apparent blood loss, hidden blood loss, average blood transfusion, and the number of cases of blood transfusion were compared between the two groups. Although there was no difference in the transfusion rate between the two groups (Fig. 2, $P = 0.826$), the observation group reported lower apparent blood loss, hidden blood loss, and average blood transfusion compared with the control group (Table 2, $P < 0.001$).

Local Application Had Higher Hct and Hb Levels and Lower CRP and Il-6 Levels than Intravenous Application

On POD 1, 2, 3, 7, and 10 the Hct and Hb of the two groups were compared, and the Hct and Hb of the observation group were higher than those of the control group (Table 3, $P < 0.05$ or 0.001).

The levels of CRP and IL-6 in the observation group were compared with the control group on POD 1, 3, 7, and 10, and the levels of CRP and IL-6 in the observation group were lower than those in the control group (Table 4, $P < 0.05$ or 0.001).

Table 1 Comparison of general data in the two groups

Group	Age (year)	BMI (kg/m^2)	ASA 3 or 4 (case)	HSS score (points)	Sex ratio (male/female)	Surgery time (min)	Cut length (cm)
Observation group (n = 36)	67.98 ± 8.87	23.86 ± 2.38	9	49.47 ± 8.91	16/20	78.06 ± 2.09	14.93 ± 2.01
Control group (n = 36)	66.98 ± 9.01	23.41 ± 2.01	10	49.03 ± 7.93	15/21	78.68 ± 2.31	14.32 ± 1.98
χ^2/t	0.475	0.867	0.071	0.221	0.057	− 1.194	1.297
P	0.636	0.389	0.789	0.826	0.812	0.236	0.199

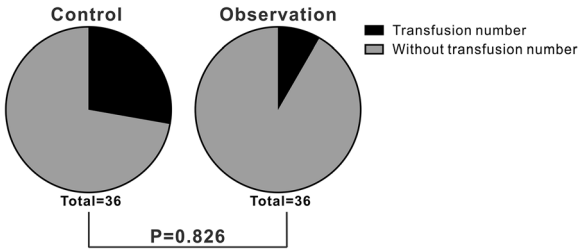

Fig. 2 Comparison of the transfusion rate

There Was No Significant Difference in Incidence of Deep Venous Thrombosis and Pulmonary Embolism Between Two Groups

On POD 7, there were one case of leg intermuscular vein thrombosis in the observation group and two cases in the control group. All the patients had no significant clinical symptoms. After symptomatic treatment, the embolus disappeared and no pulmonary embolism occurred. There was no significant difference in the incidence of deep venous thrombosis between the two groups (control vs observation 5.56% vs 2.78%, χ^2 = 0.348, P = 0.555) (Fig. 3).

In addition, in terms of length of hospital stay, we found that the average length of hospital stay in the observation group was 7.69 ± 1.21 days, and that in the control group was 9.86 ± 1.87 days. The length of hospital stay in the observation group was significantly less than that in the control group (t = − 5.846, P < 0.001).

DISCUSSION

Total hip arthroplasty can relieve the pain of patients with advanced hip disease, restore the

Table 2 Comparison of blood loss, average blood transfusion, and the number of cases of blood transfusion between the two groups

Group	Dominant blood loss (mL)	Hidden blood loss (mL)	Average blood transfusion (mL)	Cases of blood transfusion (%)
Observation group (n = 36)	958.98 ± 8.87	346.86 ± 12.38	401.29 ± 15.87	3 (8.33)
Control group (n = 36)	979.99 ± 9.01	361.41 ± 10.01	421.98 ± 16.93	10 (27.78)
χ^2/t	− 9.97	− 5.483	− 4.833	0.221
P	< 0.001	< 0.001	< 0.001	0.826

Table 3 Comparison of Hct and Hb between the two groups after the operation

Group	Hct (g/L)					Hb (%)				
	1 day after operation	2 days after operation	3 days after operation	7 days after operation	10 days after operation	1 day after operation	2 days after operation	3 days after operation	7 days after operation	10 days after operation
Observation group (n = 36)	101.09 ± 8.97	98.71 ± 5.73	96.83 ± 4.73	96.13 ± 3.87	96.02 ± 3.76	35.02 ± 2.12	34.13 ± 3.54	33.71 ± 2.65	33.56 ± 2.31	33.49 ± 2.26
Control group (n = 36)	92.08 ± 7.82	91.76 ± 4.73	87.99 ± 3.87	87.46 ± 3.79	87.41 ± 3.65	33.08 ± 2.76	32.26 ± 2.81	31.23 ± 2.32	31.18 ± 1.29	31.07 ± 1.17
t	4.543	5.612	8.679	9.604	9.858	3.345	2.482	4.293	5.397	5.776
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.001	0.015	< 0.001	< 0.001	< 0.001

Table 4 Comparison of CRP and IL-6 levels between the two groups after the operation

Group	CRP (mg/L)					IL-6 (ng/L)				
	Before operation	1 day after operation	3 days after operation	7 days after operation	10 days after operation	Before operation	1 day after operation	3 days after operation	7 days after operation	10 days after operation
Observation group (n = 36)	4.68 ± 0.35	24.02 ± 3.63	26.62 ± 3.01	26.96 ± 3.22	27.11 ± 3.31	8.76 ± 0.42	28.79 ± 3.54	21.08 ± 2.37	20.91 ± 2.41	20.68 ± 2.56
Control group (n = 36)	4.61 ± 0.31	26.08 ± 2.87	32.08 ± 2.16	32.87 ± 2.21	33.21 ± 3.01	8.67 ± 0.36	31.87 ± 2.81	25.03 ± 2.11	24.87 ± 2.04	24.76 ± 1.96
t	0.898	− 2.671	− 8.778	− 9.08	− 8.181	0.348	− 4.089	− 7.469	− 7.544	− 7.593
P	0.372	0.009	< 0.001	< 0.001	< 0.001	0.73	< 0.001	< 0.001	< 0.001	< 0.001

function of the hip joint, and improve the quality of life of patients. However, the total perioperative blood loss of total hip arthroplasty can be as high as 1683 mL, and a large amount of surgical bleeding will increase the risk of surgery and delay the recovery after surgery. Simultaneous transfusion of allogeneic blood may increase the risk of infection and the cost of treatment. TXA has been proven to be effective in reducing perioperative blood loss in total hip arthroplasty, reducing the rate of postoperative blood transfusion, while not increasing the risk of thromboembolism, conducive to patient recovery. The main methods of TXA use include topical medication, intravenous drip, etc. But at present, there is no consensus standard on the use of TXA in total hip arthroplasty. According to several clinical studies [9], 15 mg/kg TXA can be injected intravenously at the beginning of surgery, while another study [10] suggests that single use of 1 g and 20 g TXA should be considered at the beginning of total hip arthroplasty. Several clinical studies [11] suggest that 15 mg/kg TXA should be used before the operation and after an interval of 8 h. Miao et al. [12] demonstrated that the use of TXA intravenous infusion during knee catheterization reduced blood loss and transfusion without increasing the risk of venous thrombosis compared with saline intravenous infusion alone. Good et al. [13] also confirmed that the transfusion rate in the TXA group was significantly lower than that in the control group, and there was no significant difference in the incidence of deep venous thrombosis between the two groups. Yang et al. [14] suggested that there was no significant difference in the likelihood of deep vein thrombosis between the TXA group and placebo group. However, Machin et al. [15] suggested that intravenous drip or local medication could reduce postoperative bleeding in total hip arthroplasty, and there was no significant difference between the two different medication delivery methods in reducing the amount of bleeding. With years of clinical experience, the author designed the current study according to the following aspects: (1) on the basis of the safety of patients, the effects of drug should be ensured; (2) the scientific and mechanical rationale of the use time was determined on the basis of ensuring the clinical effect; (3) different applications of the drug were compared to find the best approach; (4) economic benefit should be achieved in order to decrease the cost of hospitalization. Therefore, finding the best application of TXA can improve the prognosis of patients and reduce the cost of hospitalization.

When preparing the acetabular side and enlarging the medullary cavity in the first total hip arthroplasty, there is massive intramedullary and soft tissue bleeding and soft tissue bleeding, leading to massive perioperative blood loss. In this operation, there was not only apparent blood loss but also hidden blood loss. The mechanism of hidden hemorrhage remains unclear, but the pathophysiological changes of the body after hidden hemorrhage are similar to the changes in the ischemic hypoxic period of microcirculation of shock, resulting in anemia, which will prolong surgical wound healing, delay recovery of patients, and lead to an increased rate of various complications [16]. Therefore, in clinical practice, medical staff should take into account hidden blood loss after total hip arthroplasty.

Seo et al. [17] suggested that compared with intravenously administered TXA, local administration could effectively reduce the blood loss and transfusion volume in total knee arthroplasty. Alshryda et al. [18] demonstrated that topical administration not only reduced intraoperative bleeding but also did not increase the risk of venous thrombosis. The aggregated results of this study showed that two different dosages of TXA could reduce blood loss, blood transfusion, Hct, and Hb. The number of blood loss and transfusion cases in the observation group was lower than that of the control group, and the levels of Hct and Hb in the observation group were higher than those in the control group, indicating that injecting 2.0 g TXA in 10 mL normal saline after suturing the articular capsule can significantly reduce blood loss, hidden blood loss, average blood transfusion volume, the number of blood transfusion cases, and slowly reduce Hct and Hb. It may be attributed to the fact that local application of TXA can quickly reach a specific blood

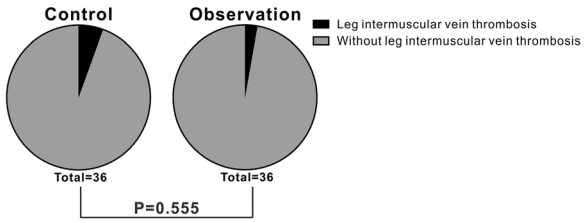

Fig. 3 Comparison of the incidence of deep venous thrombosis

concentration and function, and according to pharmacokinetic studies, 1 g TXA injection can maintain its plasma concentration above 10 mg/L for a certain time, with a half-life of 2 mL/3 h. Patients undergoing total hip arthroplasty are at high risk of deep venous thrombosis. Increased dose of TXA can lead to an increased level of plasma concentration, and the effect of fibrinolysis with TXA will result in deep venous thrombosis after the operation. Therefore, it is always important for patients with total hip arthroplasty to select the appropriate injection time and approach at the same safe dose.

In recent years, the field of orthopedics has made great efforts to promote rapid rehabilitation, and the intraoperative stress response is one of the most important aspects. The main manifestation of surgical traumatic stress is the inflammatory response of the body. The intensity of traumatic stress is determined by inflammatory mediators [19]. Hence, reducing the volume of postoperative blood loss and the rate of blood transfusion plays a vital part in the rapid recovery of patients. Numerous previous clinical studies [20, 21] have confirmed that TXA has a potential anti-inflammatory effect. On the basis of some studies supported by some scholars [22], TXA can effectively reduce the expression of inflammatory genes in perioperative patients during cardiac surgery, while other studies [23] have suggested that TXA can also reduce the inflammatory response during cardiopulmonary bypass, and the use of 2.0 g TXA injection will significantly reduce the level of IL-6. A study [24] has confirmed that the use of high-dose TXA exerts an anti-inflammatory effect. However, there are limited studies on the perioperative anti-inflammatory effect of TXA in total hip arthroplasty. On the basis of the aforementioned background, the anti-inflammatory effect of TXA was observed in this study. The results showed that the levels of CRP and IL-6 in the observation group were lower than those in the control group at POD 1, 3, 7, and 10, indicating that TXA has potential anti-inflammatory effects, and the anti-inflammatory effect of local application elicited greater beneficial results compared with intravenous application at the same dose.

Much clinical research has focused on deep venous thrombosis and pulmonary embolism caused by total hip arthroplasty. Concerns exist among doctors that the use of antifibrinolytic drugs such as TXA during the perioperative period of total hip arthroplasty will increase thrombosis [8]. There are objective and subjective factors behind this idea. Considering the invasive nature of the surgery, intraoperative and postoperative blood loss can lead to vascular rupture and indirect activation of the fibrinolytic system. Thus, there is no correlation between postoperative hypercoagulable state and TXA, and TXA does not increase the formation of a postoperative thrombus [25]. Jansen et al. [26] suggested that topical administration and intravenous administration of TXA were safe for patients with a history of lower extremity deep vein thrombosis and did not increase the risk of thrombosis. Tengberg et al. [27] reported that none of their 33 patients developed deep venous thrombosis after using TXA, but the other 39 patients who did not use TXA had two deep venous thromboses. The results of the current study showed that there was no pulmonary embolism in the observation group and the control group, and the incidence of deep venous thrombosis was comparable between the two groups, suggesting that different applications of TXA at the same dose had no association with deep venous thrombosis.

Limitations

There were several limitations in this study: (1) as a result of the small sample size of this study, blinding was not used; (2) possible systemic complications caused by intravenous application

of TXA were not observed; (3) venography is the gold standard for detection of deep venous thrombosis and pulmonary embolism, but in the present study venous color Doppler ultrasound was used; (4) our study did not explore the possible immunomodulatory effect of the inhibition of fibrinolytic enzyme activation by TXA.

CONCLUSION

The effect of local application of TXA had superior therapeutic values than intravenous application.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. XZ and JP contributed to the conception and design of the study; DM and LW performed the experiments, LW collected and analyzed data; XZ and JP wrote the manuscript; All authors reviewed and approved the final version of the manuscript.

Disclosures. Xiaodong Zhang, Desi Ma, Liang Wen and Jiang Pan have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the ethics committee of Beijing Chao-Yang Hospital, and informed consent forms were signed by patients. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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