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Original Article

Effects of general anesthesia and epidural anesthesia on deep vein thrombosis and perioperative cognitive function of patients undergoing total knee arthroplasty

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Abstract: Objective: To explore the effects of general anesthesia and epidural anesthesia on deep vein thrombosis (DVT) and perioperative cognitive function of patients undergoing total knee arthroplasty. Methods: A retrospective analysis was conducted on 110 orthopedic patients who underwent total knee arthroplasty at Zhangzhou Affiliated Hospital of Fujian Medical University from March 2018 to March 2021. According to different anesthesia schemes, 56 cases with epidural anesthesia were included in the observation group and 54 patients with general anesthesia were assigned to the control group. The following items were recorded and compared between the two groups: postoperative coagulation indicators; operation duration, total dosage of anesthetics; postoperative recovery time; heart rate (HR) and mean arterial pressure (MAP) before anesthesia induction (T0), intubation (T1), and completion of the operation (T2); cognitive function before surgery and 1 d and 3 d after surgery; postoperative incidence of DVT; pain at postoperative 24 h; stress-related factors before and 2 h after surgery, and incidence of adverse reactions during hospitalization. Results: Compared to the control group, the levels of fibrinogen (Fbg) and platelets (PLC) in the observation group 24 hours after surgery were significantly lower, with longer thrombin time (TT) and prothrombin time (PT) (all $P<0.05$); no significant difference was found in operation duration between the two groups ($P>0.05$). Total dosage of anesthetics and postoperative recovery time were less in the observation group ($P<0.05$); the HR and MAP fluctuations were lower in the observation group ($P<0.05$). The postoperative cognitive function score of patients in the observation group was significantly higher ($P<0.05$), with a lower incidence of postoperative DVT ($P<0.05$) and better relief of pain ($P<0.05$). The expression levels of stress-related factors 2 h after surgery and the incidence of adverse reactions were lower in the observation group compared to the control group ($P<0.05$). Conclusion: In total knee arthroplasty, epidural anesthesia, compared with general anesthesia, can reduce the incidence of DVT in patients and has less impact on patients' cognitive function and stress state with a higher safety profile.

Keywords: General anesthesia, epidural anesthesia, total knee arthroplasty, cognitive function, deep vein thrombosis

Introduction

With the acceleration of population aging in China, the occurrence of geriatric diseases is also increasing [1]. The prevalence of orthopedic-related diseases increases as people get older [2]. Total knee arthroplasty is one of the commonly used methods for repairing osteoarthritis in clinical practice, and it mainly uses artificial joints to replace the injured knee joints of patients, so that they can regain knee joint function [3, 4]. With the continuous advances in artificial joint technology, artificial total knee replacement has been widely used in bone and joint surgery. However, due to the irreversible aging process and decline in physical fitness, patients get susceptible to multiple postoperative complications, mainly including infection, lower limb deep vein thrombosis (DVT), prosthetic loosening, and patella osteoarthritis [5].

DVT is a serious complication after total knee arthroplasty, with phlebitis and lower limb swelling and pain as the main clinical manifestations. If not handled properly, it easily causes

pulmonary embolism, which is debilitating and fatal [6]. According to a report, the incidence of DVT after total knee arthroplasty is as high as over 50% [7]. In addition, postoperative cognitive dysfunction is also a common surgical complication, which may affect postoperative functional recovery, prolong the length of hospital stay, and even continuously affect the postoperative quality of life of patients [8]. Therefore, how to effectively reduce the occurrence of postoperative DVT and cognitive dysfunction of patients undergoing total knee arthroplasty is an urgent problem. The reasons for DVT formation after total knee arthroplasty are complicated, and different anesthesia methods have also been confirmed to have an impact on DVT formation [9]. At present, the commonly used anesthesia methods for total knee arthroplasty are epidural anesthesia and general anesthesia, both of which have a certain influence on patients' coagulation function [10]. However, there are relatively few studies on how general anesthesia and epidural anesthesia would affect the DVTs and perioperative cognitive function of patients undergoing total knee arthroplasty.

Therefore, this study investigated the effects of general anesthesia and epidural anesthesia on cognitive dysfunction and DVT, hoping to provide a more reliable anesthesia management plan for patients undergoing total knee arthroplasty.

Materials and methods

Clinical information

In this retrospective study, the clinical data of 110 patients with osteoarthritis who underwent total knee arthroplasty at Zhangzhou Affiliated Hospital of Fujian Medical University from March 2018 to March 2021 were analyzed. According to different anesthesia schemes, patients were divided into an observation group with 56 cases (using epidural anesthesia program) and a control group with 54 cases (using general anesthesia program). Inclusion criteria: (1) Patients who underwent total knee replacement surgery. (2) Patients without DVT confirmed by preoperative color Doppler ultrasound or relevant examinations. (3) Patients with ASA grades 1-3. (4) Patients who received MMSE score evaluation. (5) Patients who received norepinephrine (NE) and cortisol (Cor) tests. Exclusion criteria: (1) Those with severe liver and kidney dysfunction; (2) Those with coagulation dysfunction; (3) Those with DVT before surgery; (4) Those with malignant tumor(s); (5) Those with expression disorder or cognitive impairment. All patients agreed to participate in this study and provided their written consent. This study was reviewed and approved by the Ethics Committee of Zhangzhou Affiliated Hospital of Fujian Medical University (2021KYZ279) and was conducted in conformity with the Declaration of Helsinki.

Anesthesia

Both groups of patients underwent artificial total knee arthroplasty performed by the same group of physicians, anesthesiologists, and nursing staff. After entering the operating room, the veins of the patient were opened; ambulatory electrocardiogram, pulse oximetry monitoring, and central venous pressure monitoring were performed and the bispectral index of EEG was measured to maintain hemodynamic stability during the operation.

The control group was given general anesthesia, specifically as follows: Diazepam (0.2 mg/kg; Shanxi Zhendong Ante Biopharmaceutical Co., Ltd., China, SFDA Approval Number: H14022662), propofol (1.5 mg/kg; Guangdong Jiabo Pharmaceutical Co., Ltd., China, SFDA Approval Number: H20051843), fentanyl (3 μg/kg; Jiangsu Enhua Pharmaceutical Co., Ltd., China, SFDA Approval Number: H20143315), and vecuronium bromide (0.1 mg/kg; Chenxin Pharmaceutical Co., Ltd., China, SFDA Approval Number: H20067458) were used as anesthesia induction for rapid intravenous induction, and tracheal intubation was performed upon the completion of anesthesia induction. During the operation, nitrous oxide (Beijing Praxair Gas Co., Ltd., China, SFDA Approval Number: H11022587), vecuronium, and isoflurane were selected as anesthesia maintenance drugs, and fentanyl was added depending on individual conditions, with the depth of anesthesia controlled between 45-65 Bispectral Index (BIS).

Patients in the observation group were given epidural anesthesia as follows: The catheter was inserted into the head about 3 cm through the puncture made through the interspace of L2-3, and 8-20 mL 0.25% dicaine + 1% lido-

caine was injected through the catheter (Hunan Zhengqing Pharmaceutical Group Co., Ltd., China, SFDA Approval Number: H43021930). After the onset of epidural anesthesia, patients in observation group were given the same general anesthesia operation as control group, and the doses of propofol and fentanyl injection were controlled at 3 mg/kg and 0.2 μmg/kg per minute to maintain the anesthesia effect, then it was followed with indirect injection of vecuronium bromide. Additional intraoperative dosage could be appropriately increased according to the requirements of the anesthesia plane. Heart rate (HR), mean arterial pressure (MAP), blood oxygen saturation (SpO_2) and respiratory rate (RR) were routinely monitored in both groups. All patients were given low molecular weight heparin (LMWT) (manufactured by GlaxoSmithKline, specification 4100 IU: 0.4 mL, product batch number 15035002), 0.2 mL/time, 1 time/d. Three days later, the dose was adjusted to 0.4 mL/d for a total of 10 days of injection. Then, anticoagulation, related pain management, and postoperative walking training after surgery were provided subsequently.

Specific measures for pain management were as follows: The patients were promptly asked if there was any discomfort when they got conscious and told not to worry too much. After operation, flurbiprofen axetil injection (100 mg) was given intravenously, twice a day, continuously for 3 days after operation.

Specific measures of walking training were as follows: Walking training was conducted after the patients could successfully stand at the bedside for more than 30 minutes without discomfort. During training, the patients were told to try their best to support the upper extremity to relieve the weight-bearing of the lower extremity. The patients were instructed to use the walker correctly in the first 1-2 weeks, and then use the crutches after gaining a sense of balance until the restoration of full strength and balance.

Outcome measures

Main outcome measures: (1) Cognitive function of patients in the two groups was compared before and 1 d and 3 d after surgery using the Mini-Mental State Examination Scale (MMSE) [11]. The MMSE scale has a full score of 30 points with a total of 19 items including time orientation, location orientation, immediate language memory, short-term memory, attention and calculation, object naming, reading comprehension, language retelling, speech expression, and language comprehension. Higher score indicate better cognitive function. (2) The incidence of postoperative DVT of two groups was compared. Patients with venous thrombosis would experience sudden swelling of the lower extremities, possibly lower extremity pain and obvious lower extremity tenderness. (3) Peripheral venous blood (5 ml) was drawn from patients before and 2 h after the operation, and the levels of stress-related factors, including norepinephrine (NE) and cortisol (Cor) were detected using a Beckman automatic immune analyzer.

Secondary outcome measures: (1) The coagulation indexes of patients in the two groups 24 h after surgery were tested and compared using a fully automatic coagulation analyzer, including fibrinogen (Fbg), platelet (PLC), thrombin time (TT), and prothrombin time (PT). (2) The operation duration, total dosage of anesthetics, and postoperative recovery time were compared between the two groups. (3) The hemodynamic changes of the two groups of patients before anesthesia induction (T0), intubation (T1) and completion of the operation (T2) were monitored and compared, including MAP and HR. (4) The Numerical Pain Score (NRS) [12] was used to assess the postoperative pain of patients. On a 0-10-point scale, higher scores indicate more severe pain. (5) The incidence of adverse reactions, including respiratory depression, nausea and vomiting, infection, and lethargy, were recorded and compared between the two groups.

Statistical methods

SPSS 18.0 statistical software (Beijing Wangshu Times Technology Co., Ltd.) was used for statistical analysis of the data, and GraphPad 6 was used for image rendering. Counted data were recorded in the form of number of cases and percentages (%). For measured data, the inter-group comparison and intra-group comparison were performed by independent t-test and paired sample t-test. Data comparisons at different time points after treatment were performed using repeated measures ANOVA, and post hoc test was performed with LSD/t test, respectively. $P<0.05$ was regarded as statistically significant.

Table 1. General information [n (%)]

Factor	Observation Group (n=56)	Control Group (n=54)	t/X^2	P
Gender			0.033	0.857
Male	30 (53.57)	28 (51.85)		
Female	26 (46.43)	26 (48.15)		
Age (years)			0.157	0.692
≤67	27 (48.21)	24 (44.44)		
>67	29 (51.79)	30 (55.56)		
BMI (kg/m^2)			0.0004	0.983
≤23	31 (55.36)	30 (55.56)		
>23	25 (44.64)	24 (44.44)		
History of smoking			0.001	0.972
YES	23 (41.07)	22 (40.74)		
NO	33 (58.93)	32 (59.26)		
Primary disease			0.363	0.834
Rheumatoid arthritis	21 (37.50)	20 (37.04)		
Osteoarthritis	19 (33.93)	16 (29.63)		
Traumatic arthritis	16 (28.57)	18 (33.33)	0.129	0.898
Underlying disease				
Coronary Heart Disease	34 (60.71)	31 (57.41)	1.679	0.195
Hypertension	31 (55.36)	32 (59.26)	0.171	0.679
Diabetes	28 (50.00)	25 (46.30)	0.232	0.630

Results

Comparison of general information

The two groups of patients were comparable as there were no significant differences in gender, age, or smoking history (P>0.05) **Table 1**.

Comparison of operation duration, total dosage of anesthetics, and postoperative recovery time

No significant difference was found in terms of operation duration between the two groups (P>0.05), while the total dosage of anesthetics and postoperative recovery time in the observation group were lower than those in the control group (P<0.05) **Table 2**.

Comparison of coagulation indexes between the two groups 24 h after operation

After epidural anesthesia and general anesthesia, the coagulation indexes were detected in both groups. It was found that the levels of fibrinogen (Fbg) and platelets (PLC) in the observation group were significantly lower than those in the control group, while the thrombin time (TT) and prothrombin time (PT) were significantly longer (P<0.05) **Table 3**.

Comparison of MAP and HR between the two groups at different time points

HR and MAP showed no significant differences between the two groups at T0 (P>0.05). At T1 and T2, HR and MAP in the control group were higher than those in the observation group at the same time point (P< 0.05) **Figure 1**.

Comparison of the cognitive function between the two groups before and after operation

The comparison of MMSE scores revealed no statistical difference between the two groups before surgery (P> 0.05). At postoperative day 1 and 3, the MMSE scores of the observation group were significantly higher than those of the control group (P<0.05) **Table 4**.

Comparison of the incidence of postoperative DVT

There were 6 patients in the observation group who developed DVT with an incidence of 10.71%. In the control group, 21 patients developed DVT with an incidence of 38.89%. The incidence of postoperative DVT in the observation group was significantly lower than that in the control group (P<0.05) **Table 5**.

Comparison of postoperative pain between the two groups

At 1 h postoperatively, no significant difference was observed in NRS scores between the two groups. At 6 h and 12 h after operation, the NRS scores of the observation group decreased compared to the control group (P<0.05) **Table 6**.

Comparison of stress-related factors before and 2 h after operation between the two groups

At 2 h after operation, the levels of stress-related factors NE and Cor increased in both groups

Table 2. Comparison of operation duration, total dosage of anesthetics, and postoperative recovery time

Factor	Observation Group (n=56)	Control Group (n=54)	t	P
Operation duration (min)	151.78±3.89	164.28±4.55	15.51	<0.001
Total dosage of anesthetics (mg)	286.12±17.48	350.06±15.14	20.48	<0.001
Postoperative recovery time (min)	18.6±3.75	32.99±3.58	20.57	<0.001

Table 3. Comparison of coagulation indexes between the two groups 24 h after surgery

Index	Observation Group (n=56)	Control Group (n=54)	t	P
Fbg (g/L)	3.25±0.35	3.9±0.22	11.61	<0.001
PLC (×10^9)	197.51±27.9	253.78±26.75	10.79	<0.001
TT (s)	23.37±4.8	18.38±2.51	6.80	<0.001
PT (s)	15.15±2.48	12.2±1.16	7.94	<0.001

Note: Fbg: fibrinogen; PLC: platelets; TT: thrombin time; PT: prothrombin time.

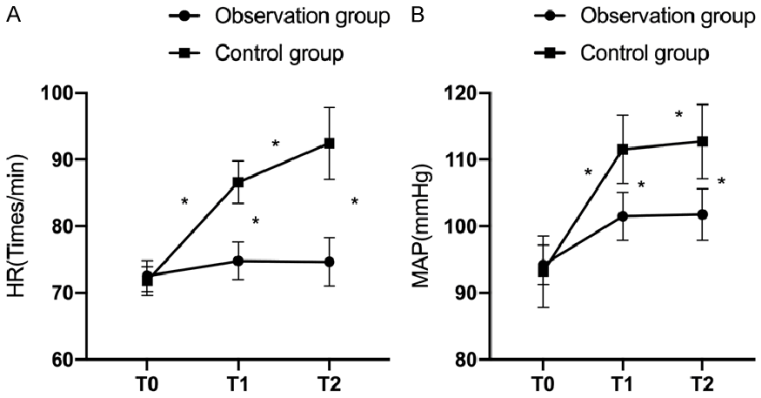

Figure 1. Comparison of HR and MAP between the two groups at different time points. A: Comparison of HR between the two groups at different time points; B: Comparison of MAP between the two groups at different time points. * indicates P<0.05.

Table 4. Comparison of cognitive function between two groups before and after surgery

Time of testing	Observation Group (n=56)	Control Group (n=54)	t	P
Before Operation	28.38±1.22	28.14±1.2	1.040	0.301
1 d after operation	24.28±1.3	20.23±1.06	17.87	<0.001
3 d after operation	27.85±1.12	24.29±0.98	17.72	<0.001

Table 5. Comparison of the incidence of postoperative deep venous thrombosis between the two groups

Item	Observation Group (n=56)	Control Group (n=54)	X^2	P
Deep vein thrombosis	6 (10.71)	21 (38.89)	11.78	<0.001
No deep vein thrombosis	50 (89.29)	33 (61.11)		

compared to those before surgery, and the levels in the observation group were lower compared to the control group (P<0.05) **Figure 2**.

Comparison of the incidence of adverse reactions between the two groups

In the observation group, there were 1, 1, 2 and 1 patients experienced respiratory depression, nausea and vomiting, infection and drowsiness respectively, with an incidence of adverse reaction of 8.93%. Those in the control group were 4, 3, 5, and 4 respectively, with an incidence of adverse reactions of 27.78%. The incidence of adverse reactions in the observation group was significantly lower than that in the control group (P<0.05) **Table 7**.

Discussion

The knee joint is an important weight-bearing joint. Once degenerative bone and joint disease occurs, it will have a huge impact on the patient's limb function and quality of life [13]. At present, artificial joint replacement has become one of the effective methods for the treatment of senile fractures and arthropathy. However, the decline in body functions gradually weakens the blood circulatory system, lead to certain fluctuations in hemodynamics during surgery and increase of

Table 6. Comparison of postoperative pain between the two groups

Time of testing	Observation Group (n=56)	Control Group (n=54)	t	P
1 h after operation	2.98±0.37	2.94±0.36	0.574	0.567
6 h after operation	3.99±0.36	4.89±0.24	15.37	<0.001
12 h after operation	3.47±0.33	4.32±0.22	15.84	<0.001

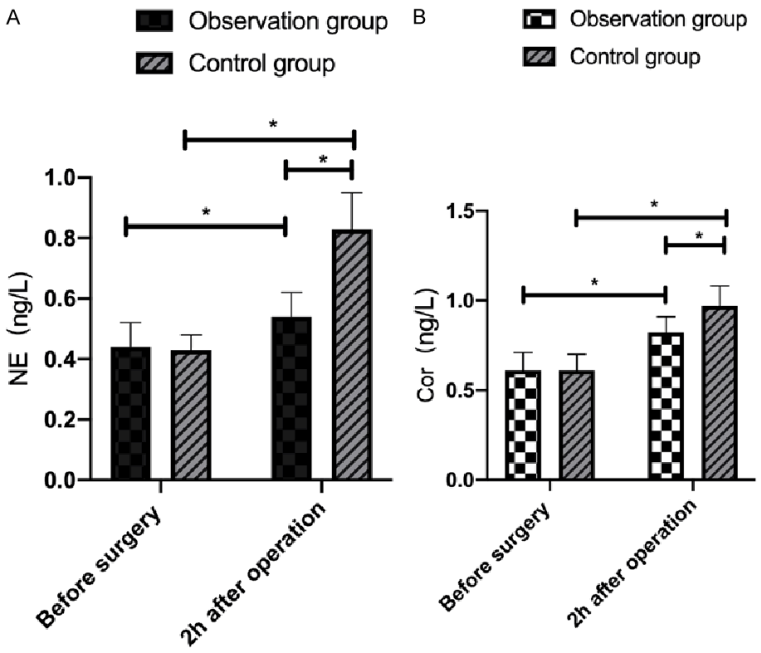

Figure 2. Comparison of stress-related factors before and 2 h after the operation between the two groups. A: Comparison of NE between the two groups before and 2 h after surgery; B: Comparison of Cor between the two groups before and 2 h after surgery. * indicates P<0.05.

Table 7. Comparison of the incidence of adverse reactions between the two groups of patients [n (%)]

Adverse reaction	Observation Group (n=56)	Control Group (n=54)	X^2	P
Respiratory depression	1 (1.79)	4 (7.41)	-	-
Nausea and vomiting	1 (1.79)	3 (5.56)	-	-
Infection	2 (3.57)	5 (9.26)	-	-
Drowsiness	1 (1.79)	3 (5.56)	-	-
Adverse reaction rate	5 (8.93)	15 (27.78)	6.566	0.010

the risk of DVT and postoperative cognitive dysfunction [14, 15]. Therefore, it is crucial to select a suitable anesthesia method for elderly patients undergoing joint replacement surgery.

At present, continuous epidural anesthesia and general anesthesia are usually used in total knee arthroplasty. As we know, different anesthesia methods have different effects on coagulation function in clinical practice [16]. Epidural anesthesia was shown to reduce the incidence of postoperative blood hypercoagulability and avoid postoperative venous thrombosis and pulmonary embolism [17]. However, some scholars believe that there is no significant difference in terms of the effects of general anesthesia and epidural anesthesia on the coagulation function of patients undergoing surgery [18]. In the present study, it was found that the levels of Fbg and PLC of the observation group were significantly lower than those of the control group, while the TT and PT were longer. In addition, the MAP and HR in the observation group were more stable at T1 and T2 compared to the control group, suggesting that epidural anesthesia can more effectively ensure the stability of hemodynamics and inhibit HR and blood pressure fluctuations in elderly patients undergoing total knee arthroplasty. This is because epidural anesthesia allows anesthetics to enter the circulatory system of patients through the epidural space, reducing the activity of PLC and thus attenuating coagulation activation [19]. There were also studies [20] that analyzed the value of epidural and general anesthesia in total knee arthroplasty, and observed that PLT, PT, and APTT of the epidural anesthesia group were drastically longer than those in patients undergoing general anesthesia, and Fbg in epidural anesthesia group was comparatively lower, which is consistent with our observations.

In this study, the total dosage of anesthetics in the observation group was less and the post-

operative recovery time was shorter compared to the control group. This may be related to high levels of inflammatory factors, which can have neurotoxic effects and cause neurodegenerative changes, ultimately affecting the cognition of patients, The decline of cognitive function may also be related to the adverse reactions of general anesthetics in the patient's body [21]. Compared with the control group, the total dosage of anesthetics in the observation group was less. In terms of postoperative cognitive function, MMSE scores were higher in the observation group 1 and 3 days after operation. This is because epidural anesthesia can reduce the dose of general anesthetics and further inhibit the toxic effects of general anesthetics on the nerves, thus reducing the risk of cognitive dysfunction in patients [22]. Epidural anesthesia has a dual blocking effect on the peripheral spinal nerves and central sympathetic nerves, which can alleviate patient's perioperative stress responses and inhibit the release of inflammatory factors, thereby protecting the cognitive function of patients [23].

The subsequent comparison of the incidence of DVTs between the two groups revealed a significantly lower incidence in the observation group, suggesting that epidural anesthesia is beneficial to reduce the occurrence of DVT. The reason may be that epidural anesthesia does not reduce the blood supply of the limbs below the block level, but increases it, thereby reducing blood viscosity and preventing venous thrombosis [24]. General anesthesia can activate platelet membrane glycoprotein to some extent, which may trigger the activation of platelet function [25]. Besides, general anesthesia affects the endocrine system of surgical patients in a certain way. Moreover, elderly patients with impaired cardiovascular system function are more sensitive to medications and are often accompanied by intense stress reactions, which may trigger platelet function activation, leading to perioperative blood hypercoagulability and adverse reactions such as DVT [26].

In addition to DVT and cognitive dysfunction, acute pain after total knee arthroplasty needs to be resolved clinically [27]. In this study, the NRS score of the observation group at 6 h and 12 h after surgery was significantly lower than that of the control group, indicating better analgesic effects of epidural anesthesia. Increased levels of NE and Cor were also observed in both groups compared with those at 2 h after the operation, but their levels were lower in the observation group compared to the control group at the same time point. The increase in NE and Cor in patients after surgery indicates that the operation has caused a certain stress response to the patient's body. Our research results suggest that epidural anesthesia is less stimulating to the body and more conducive to patients' recovery. The incidence of adverse reactions in the observation group was significantly lower than that in the control group, which also suggests that epidural anesthesia has a smaller impact on patients.

However, this study also has certain limitations. For example, we found that the coagulation function of the two groups of patients was significantly different after anesthesia, and the reason is unclear. In future studies, we will further analyze the reasons for the differences in bleeding and coagulation function of patients to find the most appropriate anesthesia method for patients undergoing total knee arthroplasty, thereby helping improve the outcome.

In summary, compared to general anesthesia, epidural anesthesia can reduce the incidence of DVT among patients undergoing total knee arthroplasty, and it has fewer adverse impacts on cognitive function and stress state of patients while maintaining a high safety profile.

Disclosure of conflict of interest

None.

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