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Original Article

Influence of epidural anesthesia and general anesthesia on thromboembolism in patients undergoing total knee arthroplasty

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Abstract: Objective: This study aimed to explore the application value of epidural and general anesthesia in total knee arthroplasty (TKA). Methods: We first retrospectively analyzed 156 patients who underwent total knee arthroplasty in our hospital from January 2019 to January 2020 as subjects. The control group (CG) included 86 subject who were treated with general anesthesia. The remaining 70 subjects with epidural anesthesia were divided to a research group (RG). The recovery and adverse reactions after surgery were compared. The coagulation function before and after surgery was analyzed. The incidence of deep vein thrombosis (DVT) after surgery was observed. The expression of inflammatory factors and the improvement of cognitive function were assessed before surgery, followed by 6 and 12 h after surgery. The pain degree of patients was compared at 6 and 12 h after surgery. Results: Compared with the CG, the recovery condition after surgery in the RG were dramatically lower, the concentrations of PLT, PT, and APTT in the RG were higher, while FBG was markedly lower. The incidence of postoperative venous thrombosis in the RG was lower. The TNF-α, IL-6 levels, and VAS scores in the RG were remarkably lower at 6 and 12 h after surgery. MMSE score was significantly higher than CG score. The total incidence of adverse reactions in the RG was markedly lower. Conclusion: Epidural anesthesia can improve blood coagulation and cognitive function in patients undergoing TKA and reduce the incidence of DVT and the degree of postoperative pain.

Keywords: Epidural anesthesia, general anesthesia, total knee arthroplasty, coagulation function

Introduction

As the prolonged longevity of the population grows, joint diseases are becoming more and more common, especially among the elderly [1, 2]. With the development of medical science and technology, total knee arthroplasty (TKA) has been more and more widely applied in clinical practice. The proportion of patients with knee joint diseases who choose artificial joint replacement treatment is rising [3]. Most of the replacements were for elderly patients whose physical function was relatively weak. The recovery of coagulation function was also slow. The injuries caused by surgery also cause more negative effects [4]. Some studies have shown that most patients have serious problems in coagulation function during perioperative period, such as venous thrombosis [5, 6]. With the increasing research on venous thrombosis, scholars have found that different anesthesia methods have different effects on deep venous thrombosis (DVT). It's particularly important to choose an appropriate anesthesia scheme.

A recent research study has revealed that under anesthesia, the cerebral blood flow of patients will be reduced, and the brain metabolism will be disturbed, which will lead to permanent changes in the central nervous system of patients for a long time [7]. Once the central nervous receptors and neurotransmitters in the body become abnormal, patients' postoperative memory would be changed, facilitating the synaptic plasticity, and affecting the signal transmission of neurons [8]. General anesthesia is one of the anesthesia methods for knee joint catheterization, but it will cause many

complications during anesthesia. This is very harmful to patients, which will cause nervous system, circulatory, and respiratory system disorders [9]. Another study has pointed out that different anesthesia methods have different effects on postoperative DVT and cognitive dysfunction [10]. Epidural anesthesia is epidural space block anesthesia. By injecting local anesthetics into the epidural space, it blocks the spinal nerve root and temporarily paralyzes the dominant area. This exerts the anesthetic effect [11]. For example, Wang W *et al.* gave epidural anesthesia and local anesthesia to patients with lumbar disc herniation. They found that patients receiving epidural anesthesia had better analgesic effect and lower incidence of postoperative adverse reactions. Their satisfaction was higher than that of those undergoing local anesthesia [12].

In this study, general anesthesia and epidural anesthesia were given to patients undergoing TKA. The effects of two different anesthesia methods on coagulation function, cognitive function, and postoperative DVT were observed, in aim to provide a better anesthesia intervention for TKA.

Materials and methods

General data

We retrospectively analyzed 156 patients who underwent total knee arthroplasty in our hospital from January 2019 to January 2020 as the study subjects. Among them, 86 were treated with general anesthesia and were included to a control group (CG). The remaining 70 with epidural anesthesia were divided into a research group (RG).

Inclusion criteria: both groups of patients met the indications of TKA [13]; patients with no history of coagulation dysfunction, venous thrombosis, or vascular surgery; patients who actively accepted and cooperated with this research; patients with complete data. This study was approved by the Ethics Committee of our hospital (SQ-700-258). Both the subjects and their families were informed in advance. They signed an informed consent form.

Exclusion criteria: patients with nervous system diseases; those complicated with severe liver and kidney function diseases; those who are allergic to narcotic drugs; those with important organ dysfunction; long-term bedridden patients; those with systemic infection; those with knee tuberculosis; those with severe hearing or visual impairment; those who quit the experiment halfway; those who accepted other treatment schemes; those who lost to the follow up.

Anesthesia intervention methods

Both groups received TKA treatment, which was completed by the same group of doctors, anesthesiologists, and nurses. Once entering the operating room, the vein was opened, and their dynamic electrocardiogram, pulse oxygen saturation, and central venous pressure were monitored. The bispectral value was measured. Patients in the CG were given general anesthesia and rapid intravenous induction. The induction drugs included diazepam 0.2 mg/kg, propofol 1.5 mg/kg (Sigma-Aldrich, Shanghai, China, Y0000017), fentanyl 3 μg/kg (Nhwa Pharmaceutical Co., Ltd., Jiangsu, China, H20-123297), and vecuronium 0.1 mg/kg (Tiantaishan Pharmaceutical Co., Ltd., Chengdu, China, H20063411). After that, endotracheal intubation was performed, and drugs such as nitrous oxide, vecuronium and isoflurane (Keyuan Pharmaceutical Co., Ltd., Shandong, China, H19990157) were used to maintain anesthesia. It's important to choose whether to add fentanyl according to the specific conditions of patients. In the meantime, those in the RG were given epidural anesthesia; lumbar puncture and catheterization were performed in L2-3 lumbar vertebrae. After successful catheterization, place it about 3 cm to the side inclined to the head; then, 1% lidocaine and 0.25% dicaine (8-20 ml) were injected through the catheter. Finally, based on the specific requirements of anesthesia, it's necessary to judge and choose whether to continue to add anesthetic drugs during the operation.

Outcome measures

1. Anesthesia recovery: the time of spontaneous breathing recovery, eye-opening, full consciousness and extubation of patients in both groups after surgery were observed and recorded.

2. Coagulation index: 5 mL fasting venous blood was drawn from patients in both groups

Table 1. Comparison of general data between both groups [n (%)] (mean ± SD)

Category	Research group (n=70)	Control group (n=86)	t/χ^2 value	*P* value
Gender			0.040	0.841
Male	41 (58.57)	49 (56.98)		
Female	29 (41.43)	37 (43.02)		
Average age (years)	56.47±5.17	55.79±5.19	0.815	0.416
BMI (kg/m^2)	23.15±2.09	23.27±2.12	0.353	0.723
History of smoking			0.052	0.818
Yes	46 (65.71)	55 (63.59)		
No	24 (34.29)	31 (36.05)		
History of drinking			0.093	0.760
Yes	44 (62.86)	52 (60.47)		
No	26 (37.14)	34 (39.53)		
Dietary preference			0.612	0.434
Spicy	45 (64.29)	50 (58.14)		
Light	25 (35.71)	36 (41.86)		
History of sports			0.178	0.672
Yes	39 (55.71)	45 (52.33)		
No	31 (44.29)	41 (47.67)		
Primary disease			0.004	0.998
Osteoarthritis	29 (41.43)	36 (41.86)		
Rheumarthritis	22 (31.43)	27 (31.40)		
Other diseases	19 (27.14)	23 (26.74)		
Surgical site			0.049	0.823
Bilateral	37 (52.86)	47 (54.65)		
Unilateral	33 (47.14)	39 (45.35)		

the day before surgery and 24 h after surgery. Then, it was centrifuged 10 min at 1500 r/min, and stored in a refrigerator at -70°C for later use. The coagulation factors (Platelet (PLT), fibrinogen (FBG), and prothrombin time (PT), activated partial thromboplastin time (APTT)) were tested by blood coagulation analyzer HF-6000 (Hukang Centrifuge Co., Ltd., Hunan, China, HF-6000).

3. Venous thrombosis: the incidence of DVT after surgery of both groups was observed.

4. Detection of inflammatory factors: 5 mL venous blood was drawn from patients in both groups on the 1st day before surgery, 6 and 12 h after surgery, and then centrifuged at 1500 r/min for 10 min, and finally stored in -70°C refrigerator. The concentration of tumor necrosis factor-fgroups and interleukin-6 (IL-6) in serum was detected by ELISA [14] in the light of the instructions of human TNF-α and IL-6 (E-EL-H0109c, E-EL-H0102c, Wuhan, China).

5. Pain degree: the pain degree of patients at 6 and 12 h after surgery was evaluated by visual analogue scale (VAS) [15]. The total score is 10 points: the higher the score, the higher the pain level.

6. Cognitive function: the cognitive function of patients before, 6 and 12 h after surgery was assessed by the mini mental state scale (MMSE) [16] with 30 scores in total. The scale has 6 dimensions, including 10 points for orientation, 3 for memory, 5 for calculation and attention, 3 for recall capability, and 9 for linguistic SPSS22.0 (Beijing Bioeasy Technology Co., Ltd., China) was used for statistical analysis, and figures were drawn by GraphPad Prism 7. The intra-group counting data were expressed by number of cases/percentage [n (%)]. The inter-group comparison was made by Chi-square test, when the theoretical frequency was less than 5, continuous correction Chi-square test was employed. The measurement data were expressed by mean ± standard deviation (mean ± SD); the inter-group comparison was conducted by independent-samples T test, while the intra-group comparison of before and after surgery was conducted by paired t test. A *P* value of <0.05 was regarded to be statistically significant.

Results

General data

There was no remarkable difference in gender, average age, body mass index (BMI), history of smoking, drinking and sports, dietary preference, primary disease, and surgical site of patients between two groups *(*all *P*>0.05) (**Table 1**).

Comparison of postoperative anesthesia recovery between two groups of patients

After comparing the recovery condition between both groups, we found that the time to sponta-

Table 2. Comparison of postoperative anesthesia recovery between both groups (mean ± SD)

Group	n	Recovery time of spontaneous breathing (min)	Opening time (min)	Fully conscious time (min)	Extubation time (min)
Research group	70	16.15±1.46	23.27±2.43	29.15±2.59	31.22±3.05
Control group	86	22.21±2.04	29.94±2.42	35.09±3.04	37.14±3.07
t	-	20.880	17.090	12.960	12.010
P	-	<0.001	<0.001	<0.001	<0.001

Table 3. Comparison of coagulation indexes between both groups before and after operation (mean ± SD)

Group	n	PLt/10^9 L^{-1}		Fbg (g/L)		PT/s		APTT/s	
		Before operation	After operation	Before operation	After operation	Before operation	After operation	Before operation	After operation
Research group	70	215.46±20.49	206.47±20.04	3.47±0.18	3.67±0.22	11.45±1.07	11.26±1.28	30.75±3.49	28.06±2.49
Control group	86	214.79±50.52	171.49±18.41	3.45±0.17	4.56±0.15	11.39±1.05	9.06±0.27	30.45±3.43	22.94±2.46
t	-	0.104	11.340	0.711	29.940	0.352	15.530	0.539	12.860
P	-	0.917	<0.001	0.477	<0.001	0.725	<0.001	0.590	<0.001

Table 4. Comparison of incidence of postoperative DVT between both groups [n (%)]

Group	n	Incidence of DVT (%)	
		Not happened	Happened
Research group	70	65 (92.86)	5 (7.14)
Control group	86	65 (75.58)	21 (24.42)
χ^2	-	-	8.292
P	-	-	0.004

neous breathing recovery, eye opening, full consciousness and extubation in the RG were markedly lower than those in the CG, with statistical significance (all *P*<0.05) (**Table 2**).

Comparison of coagulation indexes between both groups before and after surgery

The blood coagulation indexes of both groups before and after the operation were observed. There was no obvious difference in PLT, FBG, PT, and APTT expression before and after operation (*P*≥0.05). There were remarkable differences in coagulation indexes (*P*<0.05). The concentrations of PLT, PT, and APTT in the RG were higher than those in the CG after surgery, FBG was lower, with statistical differences (all *P*<0.05) (**Table 3**).

Comparison of incidence of postoperative DVT between two groups of patients

The incidence of DVT after operation in the RG was 7.14%, and that in the CG was 24.42%. It manifested that the incidence in the RG was markedly lower than that in the CG, and the difference was statistically remarkable (P<0.05) (**Table 4**).

Comparison of inflammatory factors in different time periods before and after the operation between both groups

The TNF-α and IL-6 expression in both groups had no significant difference before the operation (all *P*>0.05) but increased markedly at 6 and 12 h after operation (all *P*<0.05), and the levels at 12 h after operation were remarkably lower than those at 6 h after operation (*P*<0.05). Those in the RG were significantly lower at 6 and 12 h after operation than those in the CG (all *P*<0.05) (**Table 5**).

Comparison of pain scores in different time periods after surgery between both groups

There were differences in VAS scores between both groups in different time periods after operation (*P*<0.05). The scores at 6 h after operation were markedly higher than those at 12 h after the operation (*P*<0.05). The scores of patients in the RG at 6 and 12 h after operation were lower than those in the CG (*P*<0.05) (**Figure 1**).

Comparison of cognitive function between both groups in different time periods before and after the operation

There was no marked difference in MMSE scores between the two groups before surgery

Table 5. Comparison of inflammatory factors in different time periods before and after operation between the two groups (mean ± SD)

Group	n	TNF-α (ng/L)			IL-6 (ng/L)		
		Before operation	Six hours after operation	Twelve hours after operation	Before operation	Six hours after operation	Twelve hours after operation
Research group	70	89.45±8.17	185.14±10.46	150.46±11.46	11.04±1.08	26.51±2.17	19.29±1.24
Control group	86	89.74±8.22	243.46±20.11	194.46±12.97	11.17±1.12	34.98±3.45	26.72±1.04
t	-	0.219	21.960	22.190	0.732	17.860	40.700
P	-	0.826	<0.001	<0.001	0.464	<0.001	<0.001

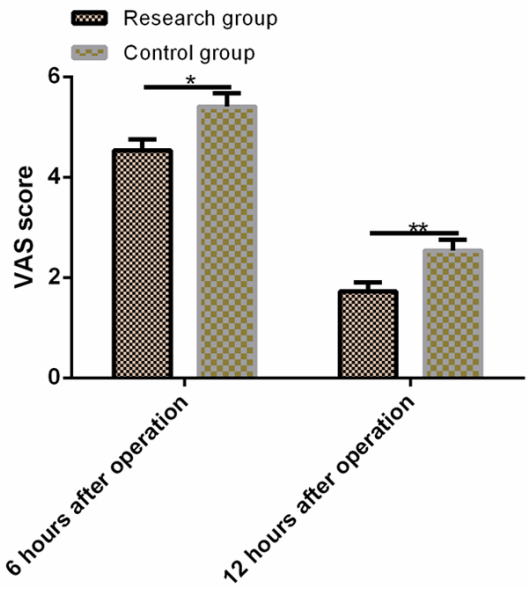

Figure 1. Comparison of pain scores between both groups at different time periods after surgery. The VAS scores of patients in the two groups are dramatically higher at 6 h and 12 h after operation, and the scores of patients in the RG at 6 h and 12 h after operation are lower than those in the CG. Note: in comparison between both groups, * <0.05; in comparison between different time periods, ** <0.01.

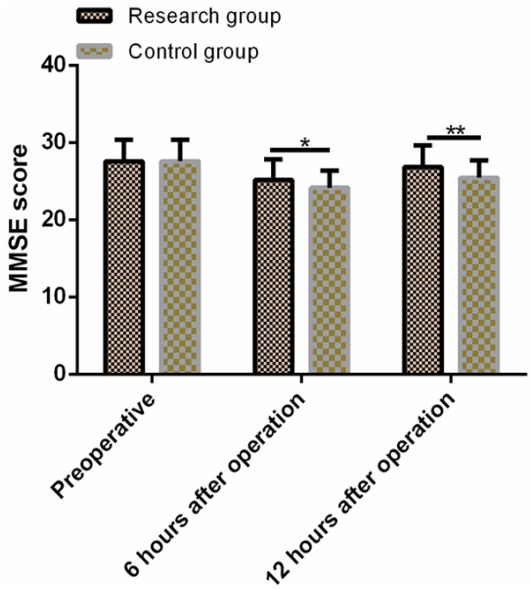

Figure 2. Comparison of cognitive function between both groups at different time periods before and after operation. There is no remarkable difference in MMSE scores between the two groups before operation, but the scores of the RG at 6 and 12 h after operation are dramatically higher than those of the CG. Note: in comparison between both groups, * <0.05; in comparison between different time periods, ** <0.01.

(*P*>0.05). The scores at 6 and 12 h after surgery were lower than those before (*P*<0.05), but the MMSE scores at 6 h and 12 h after surgery in OG were higher than those of CG (*P*< 0.05) (**Figure 2**).

Comparison of postoperative adverse reactions between two groups of patients

The postoperative adverse reactions of the two groups were observed. The results showed that the incidence in the OG was 11.43%, and that in the CG was 33.72%. Compared with the CG, the total incidence of postoperative adverse reactions in the RG was markedly lower (*P*< 0.05) (**Table 6**).

Discussion

TKA is an effective intervention for treating advanced osteoarthritis and rheumatoid arthritis and joint function reconstruction [17]. It can effectively correct the deformity of hip joints and improve the viability of patients [18]. It has a longer operation time to avoid large wounds and massive hemorrhages during the operation [19]. Due to the decline in functions of various organs of the body, the tolerance of middle-aged and elderly patients reduces, increasing the risk of operation and postoperative complications, even affecting the prognosis of patients [20].

Table 6. Comparison of postoperative adverse reactions between both groups [n (%)]

Category	Research group (n=70)	Control group (n=86)	χ^2 value	*P* value
Pain	4 (5.71)	8 (9.30)	0.699	0.402
Nausea	2 (2.86)	9 (10.47)	3.408	0.064
Vomiting	1 (1.43)	7 (8.14)	3.572	0.058
Dysphoria	1 (1.43)	5 (5.81)	2.007	0.156
Total incidence rate	8 (11.43)	29 (33.72)	10.601	0.001

A study compared the general anesthesia and spinal epidural anesthesia on elderly patients with hip replacement. The results suggested that the two kinds of anesthesia could both maintain good anesthesia effect, but spinal epidural anesthesia could shorten the onset time, exerting little effect on the hemodynamics of patients and low incidence of postoperative complications [21]. In this study, patients undergoing TKA were given epidural anesthesia or general anesthesia. It was found that the postoperative recovery of patients under epidural anesthesia was markedly higher than those under general anesthesia. For example, Fu M and Li D gave general anesthesia and epidural anesthesia to pregnant women with dystocia. The results revealed that the recovery of postoperative anesthesia of patients receiving epidural anesthesia was dramatically better than that of general anesthesia, and that of MMSE scores and vital signs at different time points after the operation in the former was improved [22]. The time to spontaneous breathing recovery, eye-opening, full consciousness and extubation in the RG were markedly shorter than those in the CG. This is also like the results of Fu M and Li D's study, indicating that epidural anesthesia can effectively reduce the dosage of general anesthesia drugs, reducing the accumulation of general anesthesia drugs in the body and the incidence of respiratory depression and other adverse conditions, and shortening the speed of postoperative analepsia. Another recent study has shown that local anesthetics can inhibit platelet function, such as inhibiting platelet aggregation and release of platelet value particles. It may also block thrombus A2 signal transduction pathway, inhibiting coagulation function [23]. These findings show, the expression concentrations of PLT, PT, and APTT in the RG are higher than those in the CG, and Fbg was markedly lower. This indicates that general anesthesia may activate platelet membrane glycoprotein, promoting platelet aggregation. In the process of epidural anesthesia, anesthetic drugs were absorbed into the blood through the epidural space, reducing the aggregation, release, and adhesion of platelets, and improving the coagulation function of patients. A recent research has revealed that TKA is an effective method to treat advanced knee joint diseases. Some complications will occur after receiving this operation, because patients are usually in hypercoagulable state and prone to thrombosis. If the treatment and intervention are not appropriate, they will be treated with venous thromboembolism [24]. Lou F *et al.* gave epidural anesthesia intervention for patients undergoing breast reconstruction with free skin flap [25], and found that it could reduce postoperative pain, side effects, and postoperative flap thrombosis [26]. This study manifested that the incidence of postoperative venous thrombosis in the RG was markedly lower than that in the CG. This may be due to general anesthesia that can bring about reduced blood flow in the lower extremity, increasing the formation of DVT. Epidural anesthesia could effectively dilate blood vessels, increase blood flow of lower limbs, and prevent thrombosis.

Another study has shown that perioperative inflammatory factors can further trigger the target cells to release secondary inflammatory mediators, to act as primary inflammatory mediators [27]. TNF-α and IL-6 are both important pro-inflammatory factors in the body. They are also one of the key markers of systemic inflammatory response after surgical trauma. Their increase is related to various postoperative complications, such as cognitive dysfunction [28]. This study manifested that the TNF-α and IL-6 expression in the RG was markedly lower than that in the CG at 6 and 12 h after operation. This indicates that after anesthesia, the surgical trauma will cause stress and inflammatory reaction. The increase of inflammatory factors in the RG is dramatically better than that in the CG. It also reveals that epidural anesthesia can effectively alleviate the inflammation caused by surgical trauma in TKA. Pa-

tients receiving orthopedic surgery are concerned about postoperative pain [29]. While postoperative pain is also a common problem after surgery, which not only affects the quality of life of patients, but also leads to the increase of blood glucose and blood pressure. The wounds after surgery are difficult to heal [30]. Zhang L *et al.* gave epidural anesthesia intervention for patients undergoing percutaneous endoscopic discectomy and discovered that it could markedly reduce the pain degree, mean arterial pressure, and heart rate [31]. This study also showed that the VAS scores of patients in the RG were markedly lower than those in the CG at 6 and 12 h after operation. This is also to the results of Zhang L, indicating that epidural anesthesia can effectively restrain pain stimulation and reduce postoperative pain. Postoperative cognitive dysfunction is also a familiar complication of patients after surgery, which is related to the delay of hospitalization and inability to face it independently. It shows that inflammatory factors and postoperative pain will lead to cognitive dysfunction [32]. This study manifested that the MMSE scores of patients in the RG at 6 and 12 h after surgery were higher than those in the CG. Epidural anesthesia could reduce the cognitive dysfunction of patients undergoing TKA to a certain extent, which might be due to the reduction of the release of inflammatory factors in operation and the postoperative pain. In the end, we observed the occurrence of postoperative adverse reactions. It showed that the total incidence of postoperative adverse reactions in the RG was dramatically lower than that in the CG. It also revealed that epidural anesthesia was safer than general anesthesia.

Although this study confirmed that epidural anesthesia could bring better benefits to patients undergoing TKA, but there are still some room for improvement. For example, we can include more inflammatory factors to confirm whether epidural anesthesia can really alleviate the inflammatory response caused by TKA. Further analyze the risk factors that affect the efficacy of patients. Epidural anesthesia combined with general anesthesia intervention can also be included to observe the efficacy of TKA. In the future, they will be explored in depth.

Epidural anesthesia can improve blood coagulation and cognitive function in patients undergoing TKA and reduce the incidence of DVT and the degree of postoperative pain.

Disclosure of conflict of interest

None.

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