

Received: 2017.03.16
Accepted: 2017.06.01
Published: 2018.01.04

Effects of Inhalation Anesthesia vs. Total Intravenous Anesthesia (TIVA) vs. Spinal-Epidural Anesthesia on Deep Vein Thrombosis After Total Knee Arthroplasty

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF G **Lu-Yang Zhou**
ABCDEF G **Wei Gu**
ABCDEF G **Yun Liu**
ABCDEF G **Zheng-Liang Ma**

Department of Anesthesiology, Gulou School of Clinical Medicine, Nanjing Medical University, Nanjing, Jiangsu, P.R. China

Corresponding Author: Zheng-Liang Ma, e-mail: zhenglm1117@126.com
Source of support: Departmental sources

Background: The objective of the present study was to evaluate the varying efficacy of general anesthesia (GA), combined spinal-epidural anesthesia (CSEA), and total intravenous anesthesia (TIVA) on the occurrence of deep vein thrombosis (DVT) following total knee arthroplasty (TKA).





Material/Methods: From July 2013 to May 2015, a total of 197 cases of patients who had undergone TKA treatment at either the Drum Tower Hospital or Nanjing General Hospital of Nanjing Military Command were recruited to participate in the study. The patients in the study were separated into 3 groups depending on the anesthesia approach received: the GA group, the CSEA group, and the TIVA group. The baseline characteristics and relative parameters of patients were monitored before and after surgery for analytic purposes. A 3-month follow-up after surgery was conducted to observe the rate of DVT occurrence and any DVT-related complications.

Results: The TIVA group exhibited significant decreases in relation to the swallowing time reflex, extubation, and consciousness recovery in comparison to other groups in the study. Additionally, platelet count was significantly decreased and there was drastic extension of the activated partial thromboplastin time (APTT) in the CSEA group and the TIVA group. There were clear differences in the incidence of DVT and its complications among the 3 groups. The TIVA group displayed the lowest incidences of DVT and DVT-related complication during the study. Based on logistic regression analysis, the type of anesthesia was utilized as an independent correlative factor for the occurrence of DVT after surgery.

Conclusions: The results obtained during the study established a clinical basis for comparative analysis of various anesthesia methods. We found that, compared with GA and CSEA, patients undergoing TIVA had a reduced rate of risk in relation to the occurrence of DVT following TKA.

MeSH Keywords: **Anesthesia • Knee Joint • Upper Extremity Deep Vein Thrombosis**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/904378>

 3628  8  —  32



Background

Total knee arthroplasty (TKA) is a surgical procedure in which the knee joints are replaced with artificial components. TKA is commonly performed on patients with arthritic ailments such as osteoarthritis and rheumatoid arthritis [1]. Decades of clinical treatment have proven this method to be a clinically efficacious and cost-effective intervention, yielding high rates of success for pain reduction and functionality improvement [2]. It has been projected that by 2020, total knee arthroplasty utilization will exceed one million procedures annually in the USA [3]. Following a TKA operation, the vast majority of patients have invariably displayed varying degrees of improvement in activities that have enabled them to return to regular physical activities, such as tennis, skiing, bicycling, farming, and even construction work [4]. Owing to such successful outcomes, the demand for primary TKA is projected to exponentially increase over the next few years [5]. TKA procedures are often performed under anesthesia. This has many advantages, including convenience for patients by reduced hospitalization and shorter rehabilitation. However, this type of procedure involves risks of varying degrees, depending on the patient's general health [6]. Despite the fact that TKA has helped revolutionize the life quality of patients with end-stage knee arthritis, due to various complications, some are unsatisfied with the outcomes of their procedures [7].

Venous thromboembolisms pose a major and, at times, fatal complication to patients undergoing major orthopedic surgery such as TKA [8]. It is estimated that approximately 200 000 outpatients are diagnosed with deep vein thrombosis (DVT) every year, while a large number of outpatients eventually develop DVT that are yet to be diagnosed [9]. Furthermore, lower-extremity DVT is a serious medical condition that may cause severe disability or even death, due to the formation of a pulmonary embolism, post-thrombotic syndrome, paradoxical embolization, or even limb loss [10]. Over the years, various treatment therapies have been put forward as means to prevent and manage lower-extremity DVT, such as aspirin and systemic anticoagulation therapy, which have displayed various degrees of efficacy, but are also controversial [11,12]. Recently, it has been reported that different anesthesia methods employed in TKA result in correspondingly different postoperative responses in patients, in relation to complications such as DVT, pulmonary embolism, and respiratory depression, thus presenting a new direction for clinical and surgical study [13]. Previously conducted research reported on the effects of GA, CSEA, and TIVA during and after surgery [14–16]. Owing to the lack of studies regarding the effects of anesthesia approaches on DVT, the present study aimed to explore the effects of different anesthesia methods on the incidence of lower-extremity DVT in patients receiving TKA, to provide information that will be helpful in practical use of appropriate anesthesia in TKA.

Material and Methods

Ethical statement

The study was completed with approval from the Ethics Committee of Drum Tower Hospital and Nanjing General Hospital of Nanjing Military Command. All patients in the study signed written informed consent. All procedures in this study were in strict accordance with the principles set by the Declaration of Helsinki.

Study subjects

A total of 197 patients were recruited for the purposes of the study. Between July 2013 to May 2015, 91 males and 106 females (ages 41–79 years) with varying degrees of knee pain, deformity, walking difficulty, and other symptoms were enrolled into the study. All patients in the study were given a preoperative examination. The current conditions and medical history of all patients were obtained and their physical status was evaluated prior to the administration of anesthesia. The type of anesthesia was selected according to a variety of factors, including patient preference. If a patient was suitable for more than 2 types of anesthesia, and had no special requirements, the patient would be randomly divided into each group under the informed consent of the patient in accordance with the experimental needs of the study. The patients in the study were treated using TKA at the Drum Tower Hospital and Nanjing General Hospital of Nanjing Military Command. Patients were randomly divided into 3 different groups: the general anesthesia group (GA) (GA group, n=63), the combined spinal-epidural anesthesia group (CSEA) (CSEA group, n=67), and the total intravenous anesthesia (TIVA) with propofol and remifentanyl group (TIVA group, n=67). Inclusion criteria were: 1) patients with severe knee pain, instability, deformity, and serious obstacles to daily living activities; 2) patients without abnormalities in the lower limbs via venous ultrasound; 3) patients without any obvious surgical contraindications; and 4) patients with complete medical records. Exclusive criteria were: 1) patients who had a clear history of nervous-mental system disease or took corresponding drugs before surgery; 2) patients who were incapable of tolerating surgery due to recent infection and/or poor general physical conditions; and 3) patients who already had DVT in their lower limbs before surgery, as well as varicose veins of the lower limbs observed during a routine examination. Diagnostic criteria were: 1) frequent pains during the last month before surgery; 2) sound upon moving the joint; and 3) bony hypertrophy in knee examination (Table 1).

Therapeutic methods

The GA group: Patients were given an intravenous drip of dexamethasone (10 mg) and atropine (0.5 mg) through a venous

Table 1. Baseline characteristics of patients in the GA, CSEA and TIVA groups.

Characteristic	GA group (n=63)	GA group (n=63)	TIVA group (n=67)	P
Case	63	67	67	—
Gender (male/female)	30/33	29/38	32/35	0.841
Mean age (years)	61.30±7.85	59.55±6.30	60.90±8.51	0.405
BMI (kg/m ²)	26.60±4.16	25.90±3.43	27.10±4.71	0.243
Replacement side (left/right knee; case)	28/35	26/41	31/36	0.662
Mean disease course	9.44±3.19	10.12±2.65	9.70±3.28	0.444

BMI – body mass index; GA – general anesthesia; CSEA – combined spinal-epidural anesthesia; TIVA – total intravenous anesthesia

channel that had been previously established. Anesthesia was induced using fentanyl 2–4 µg/kg, propofol 1.5–2 mg/kg, vecuronium 0.06–0.08 mg/kg, and midazolam 0.1–0.2 mg/kg. After tracheal intubation, anesthesia was maintained via inhalation of 1.3–2% isoflurane and infusion of propofol 2–4 mg/kg/h, as well as intermittent fentanyl with a total of 4–6 µg/kg.

The CSEA group: In the lateral position, L₃₋₄ interspace served as puncture point. After the epidural puncture was achieved, 2 ml of lumbar spinal fluid (0.75% levobupivacaine 1 mL + 10% GS 1 mL) was injected. Patients in the CSEA group were treated by inhalation of pure oxygen during surgery. If patients had discomfort during surgery, 2% lidocaine (4 mL) was administered through the tube. If hypopnea occurred, the patients would be treated with ephedrine or with accelerated infusion.

The TIVA group: General anesthesia was induced with fentanyl 2–3 µg/kg, etomidate 0.2 mg/kg, midazolam 0.1 mg/kg, and cisatracurium besilate 0.1 mg/kg. Patients were treated with inhalation of pure oxygen during surgery, and anesthesia was maintained using remifentanyl 0.1–0.5 µg/kg/h and propofol 4–6 mg/kg/h via total intravenous micro pump until the surgery was completed. When the breathing pattern was restored, flumazenil 0.01 mg/kg was given. Catheter removal was performed when the patient was observed to be breathing in a smooth, unhindered manner.

Observation of relative indexes

Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and saturation of peripheral oxygen (S_pO₂) were continuously monitored using a DRAGER multi-function monitor (Drägerwerk AG & Co., Lübeck, Germany). The time points of these indexes were recorded before anesthesia was given, during anesthesia, at 30 and 60 min after anesthesia, and after the surgery was complete. The preoperative and postoperative blood cell parameters of patients in the 3 groups were also recorded. The parameters recorded included red blood

cells (RBC), hemoglobin (HGB), white blood cells (WBC), neutrophils, monocytes, and lymphocytes. Blood coagulation parameters of patients among the 3 groups were detected before surgery and on the 14th day after surgery, including platelet, plasma fibrinogen (FIB), prothrombin time (PT), and activated partial thromboplastin time (APTT). Before surgery and on the 1st, 3rd, 7th, and 14th day after surgery, venous blood was extracted from all patients. Blood viscosity (BV) and plasma viscosity (PV) were determined using the Low-Shear 40 Rheometer (Contraves Advanced Devices Sdn. Bhd., Malacca, Malaysia) and the D-dimer content was determined using an Innovance D-Dimer detector (Siemens Healthineers Co. Ltd., Shanghai, China). Three months after surgery, patients with any signs of DVT were noted and subsequently confirmed using an HP Image Point color Doppler ultrasound (Hewlett-Packard Development Company, California, USA). The effects of the respective anesthesia were evaluated as excellent if no pain during the operation process was recorded. The effects of anesthesia were evaluated as good if pain was sensed during the operation process that was tolerable and did not affect the surgery. The effects of anesthesia were evaluated as bad if obvious pain was recorded during the operation process and consequently resulted in the surgery being unable to be carried out smoothly [17].

Follow-up

All patients received a 3-month follow-up by telephone call, as well as through outpatient methods. All patients completed the follow-up process. The follow-up process was scheduled to begin as soon as patients were discharged from the Drum Tower Hospital and Nanjing General Hospital of Nanjing Military Command when they finished systemic treatment following their TKA procedures. The final follow-up was conducted in August 2015.

Statistical analysis

G*Power3.1 was used for estimation of sample size. The results of primary studies revealed a total NRS standard deviation

Table 2. Vital signs of patients in the GA, CSEA and TIVA groups at different time points.

Parameter	Group	Before anesthesia	During anesthesia	30 min after anesthesia	60 min after anesthesia	After surgery
SBP (mmHg)	GA group	142.80±16.50	133.60±15.40 [#]	126.20±18.70 [#]	111.20±22.80 [#]	117.60±14.50 [#]
	CSEA group	136.70±20.60	134.20±22.60	134.60±11.60 [*]	127.10±15.90 ^{*#}	125.60±13.50 ^{*#}
	TIVA group	139.40±21.90	137.60±25.80	142.80±23.80 ^{*&}	139.50±16.20 ^{*&}	135.70±8.50 ^{*&}
DBP (mmHg)	GA group	89.10±9.40	83.20±8.70 [#]	77.30±10.60 [#]	67.20±8.10 [#]	72.40±15.30 [#]
	CSEA group	85.60±10.70	86.20±11.30	88.70±8.60 [*]	72.30±14.20 ^{*#}	83.70±12.90 [*]
	TIVA group	84.20±15.60	84.40±13.60	86.80±7.40 [*]	85.40±16.90 ^{*&}	78.80±10.30 ^{*&}
HR (bpm)	GA group	74.40±15.50	76.30±17.70	78.40±16.40	79.50±15.70	73.40±16.70
	CSEA group	72.40±16.30	75.80±18.30	76.90±14.80	75.40±20.80	74.20±15.80
	TIVA group	73.60±18.50	78.50±15.70	75.30±13.10	77.80±18.20	70.70±19.90
SPO ₂	GA group	91.50±4.10	93.40±4.90	92.70±4.80	93.20±4.20	93.80±4.10
	CSEA group	92.20±3.70	93.80±3.50	93.20±3.80	94.10±3.60	94.40±3.70
	TIVA group	91.60±3.80	92.90±8.20	93.30±3.50	92.70±4.50	93.80±7.60

* $P < 0.05$ compared with the GA group; & $P < 0.05$ compared with the CSEA group; # $P < 0.05$ compared with before anesthesia; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; SPO₂ – saturation of peripheral oxygen; GA – general anesthesia; CSEA – combined spinal-epidural anesthesia; TIVA – total intravenous anesthesia.

of 2. A difference of 1 NRS score was detected among each group, which indicated that when equal to 0.05, 80% efficiency was obtained, based on a total sample size greater than 159 cases. Statistical analysis was performed using SPSS18.0 (SPSS Inc., Chicago, IL, USA). Measurement data are presented as mean ± standard deviation (SD) and the differences between 2 groups were compared by *t* test and paired *t* test. Enumeration data are presented by percentage and ratio, and multiple sample rates were compared using the chi-square test. A value of $P < 0.05$ was considered to be a statistically significant difference.

Results

The vital signs of patients in the GA, CSEA, and TIVA groups at different time points

The effects of anesthesia were all deemed to be satisfactory and no significant differences were displayed among the GA, CSEA, and TIVA groups. Regarding SBP, when compared with the GA group, the CSEA and TIVA groups presented no significant differences before and during anesthesia (all $P > 0.05$); however, the CSEA group showed significant differences at 30 min and 60 min after anesthesia, as well as following surgery (all $P < 0.05$). In contrast to the CSEA group, the TIVA group exhibited significant differences both in SBP after anesthesia

and after surgery (both $P < 0.05$). When compared with SBP before anesthesia, SBP at other time points were significantly different in the GA group (all $P < 0.05$) and SBP at 60 min after anesthesia and after surgery were also significantly different in the CSEA group (all $P < 0.05$), but SBP at other time points were not significantly different in the TIVA group (all $P > 0.05$). With respect to DBP, before and during anesthesia, there were no significant differences in the CSEA and TIVA groups compared with the GA group (all $P > 0.05$). Compared with the GA group, the CSEA and TIVA groups were significantly different in DBP at 30 min and 60 min after anesthesia and after surgery (all $P < 0.05$). When compared with the CSEA group, the TIVA group displayed significant differences in DBP at 60 min after anesthesia and after surgery (both $P < 0.05$). Additionally, when compared with DBP before anesthesia, DBP at other time points were significantly different in the GA group (all $P < 0.05$) and DBP at 60 min after anesthesia was significantly different in the CSEA group, but DBP at other time points in the TIVA group were not significantly different (all $P > 0.05$). There were no significant differences in HR and S_pO₂ among the 3 groups at any of the time points (all $P > 0.05$) (Table 2).

Blood cell parameters of patients in the GA, CSEA, and TIVA groups before and after surgery

There were no significant differences in the parameters analyzed before surgery among the 3 groups (all $P > 0.05$). After

Table 3. Blood cells parameters of patients in the GA, CSEA and TIVA groups before and after surgery.

Parameter	GA group		CSEA group		TIVA group	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
RBC (10 ¹² /L)	4.23±2.37	4.19±2.28	4.31±2.43	4.12±2.21	4.28±2.45	3.26±1.26**
HGB (g/L)	134.65±12.47	130.82±12.16	136.57±19.23	135.59±11.23	133.29±11.53	131.62±10.73
WBC (10 ⁹ /L)	6.21±1.45	6.78±2.33	6.65±1.63	7.66±1.74**	6.48±1.25	8.21±1.27**
Neutrophil (10 ⁹ /L)	3.17±1.04	4.22±1.16#	3.17±0.98	4.79±1.04**	3.56±1.29	5.01±1.22**
Monocyte (10 ⁹ /L)	0.44±0.21	0.59±0.14#	0.40±0.19	0.50±0.17**	0.43±0.20	0.46±0.23*
Lymphocyte (10 ⁹ /L)	1.59±0.54	1.53±0.32	1.76±0.43	1.54±0.52#	1.73±0.49	1.79±0.35*#

* $P < 0.05$ compared with the GA group; # $P < 0.05$ compared with the CSEA group; # $P < 0.05$ compared with before surgery; RBC – red blood cell; HGB – hemoglobin; WBC – white blood cell; GA – general anesthesia; CSEA – combined spinal-epidural anesthesia; TIVA – total intravenous anesthesia.

Table 4. General conditions during and after surgery in the GA, CSEA and TIVA groups.

Characteristic	GA group (n=63)	CSEA group (n=63)	TIVA group (n=67)	P
Operation time	151.37±12.33	154.26±12.37	152.52±11.69	0.393
Bleeding volume (mL)	416.23±123.54	439.18±118.27	425.64±109.75	0.533
Tourniquet time (min)	86.52±6.73	88.01±5.42	85.93±7.36	0.17
Transfusion volume (mL)	1536.85±108.24	1541.62±106.17	1533.87±98.15	0.91
Swallowing reflex time	26.32±1.35#	17.24±1.43*	12.25±1.08**	<0.001
Extubation time	20.24±1.15#	28.31±1.37*	13.01±1.26**	<0.001
Consciousness recovery time	33.26±1.28#	23.72±1.43*	18.63±1.14**	<0.001

* $P < 0.05$ compared with the GA group; # $P < 0.05$ compared with the CSEA group; GA – general anesthesia; CSEA – combined spinal-epidural anesthesia; TIVA – total intravenous anesthesia.

surgery, the CSEA and GA groups showed no significant differences in RBC, HGB, or lymphocyte count (all $P > 0.05$), but there were significant differences in WBC, neutrophil, and monocyte count (all $P < 0.05$). The TIVA and GA groups showed significant differences in RBC, WBC, neutrophil, monocyte, and lymphocyte count (all $P < 0.05$), but showed no significant differences in HGB ($P > 0.05$). The CSEA and TIVA groups showed significant differences in lymphocyte count ($P < 0.05$), but showed no differences in the other parameters (all $P > 0.05$). In the GA group, when comparing parameters before surgery, significant differences were not found in RBC, WBC, HGB, or lymphocyte counts (all $P > 0.05$), but were found in neutrophil and monocyte counts after surgery (both $P < 0.05$). In the CSEA group, before surgery, RBC and HGB were not significantly different after surgery (both $P > 0.05$), but the other parameters were all significantly different (all $P < 0.05$). In the TIVA group, in contrast to differences observed before surgery, differences in RBC, WBC, and neutrophil count were all statistically significant (all $P < 0.05$), but the other parameters were not significantly different (all $P > 0.05$ Table 3).

General conditions of patients during and after surgery in the GA, CSEA, and TIVA groups

Among the 3 groups, there were no significant differences in operation time, bleeding volume, tourniquet time, or transfusion volume during surgery (all $P > 0.05$). Post-surgery, differences in swallowing reflex time, extubation time, and consciousness recovery time were all statistically significant (all $P < 0.05$). As shown in Table 4, in contrast to the GA group, the CSEA and TIVA groups displayed significant differences in swallowing reflex time, extubation time, and consciousness recovery time (all $P < 0.05$), and there were also significant differences in these indexes between the TIVA and CSEA groups (all $P < 0.05$). Among the 3 groups, the TIVA group had the shortest swallowing reflex time, extubation time, and consciousness recovery time.

Table 5. Comparison of blood coagulation parameters of patients in the GA, CSEA and TIVA groups before and after surgery.

Parameter	GA group		CSEA group		TIVA group	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
Plt ($\times 10^9/L$)	173.35 \pm 23.43	178.85 \pm 23.18	172.78 \pm 22.53	162.35 \pm 21.55*#	165.43 \pm 19.89	168.26 \pm 18.53*
FIB (g/L)	3.78 \pm 1.06	3.63 \pm 0.74	3.65 \pm 1.12	4.03 \pm 0.91*	3.87 \pm 0.98	3.12 \pm 0.69*#
PT (s)	12.97 \pm 0.67	12.99 \pm 0.79	13.15 \pm 0.39	13.19 \pm 0.59	13.08 \pm 0.23	13.22 \pm 0.31*
APTT (s)	30.06 \pm 2.45	31.15 \pm 3.27	29.86 \pm 2.85	32.29 \pm 3.16#	29.43 \pm 2.13	33.41 \pm 2.64*#

* $P < 0.05$ compared with GA group; # $P < 0.05$ compared before surgery; FIB – plasma fibrinogen; PT – prothrombin time; APTT – activated partial thromboplastin time; GA – general anesthesia; CSEA – combined spinal-epidural anesthesia; TIVA – total intravenous anesthesia.

Table 6. Comparison of BV, PV and D-dimer content of patients in the GA, CSEA and TIVA groups before and after surgery.

Parameter	Group	Before surgery	After surgery			
			1 st day	3 rd day	7 th day	14 th day
Bv (mPa·s) 200·s ⁻¹	GA group	3.82 \pm 0.79	3.75 \pm 0.68	3.84 \pm 0.81	3.83 \pm 0.75	3.86 \pm 0.68
	CSEA group	3.87 \pm 0.72	3.79 \pm 0.65	3.83 \pm 0.74	3.91 \pm 0.82	3.88 \pm 0.77
	TIVA group	3.95 \pm 0.83	3.84 \pm 0.71	3.87 \pm 0.64	3.92 \pm 0.86	3.91 \pm 0.79
Pv (mPa·s)	GA group	1.41 \pm 0.22	1.36 \pm 0.18	1.40 \pm 0.17	1.41 \pm 0.25	1.42 \pm 0.19
	CSEA group	1.35 \pm 0.26	1.43 \pm 0.21	1.40 \pm 0.14	1.42 \pm 0.13	1.47 \pm 0.18*
	TIVA group	1.44 \pm 0.18	1.35 \pm 0.19	1.36 \pm 0.17	1.41 \pm 0.15	1.43 \pm 0.12
D-dimer (μ g/L)	GA group	181.27 \pm 15.32	178.48 \pm 14.93	181.48 \pm 15.59	180.12 \pm 13.67	180.48 \pm 15.63
	CSEA group	182.53 \pm 14.89	180.52 \pm 15.83	181.75 \pm 15.47	179.68 \pm 14.93	180.28 \pm 15.08
	TIVA group	183.85 \pm 17.56	183.73 \pm 15.74	181.63 \pm 13.89	179.68 \pm 15.59	181.55 \pm 13.46

* $P < 0.05$ compared with before surgery; BV – blood viscosity; PV – plasma viscosity; GA – general anesthesia; CSEA – combined spinal-epidural anesthesia; TIVA – total intravenous anesthesia.

Blood coagulation parameters of patients in the GA, CSEA, and TIVA groups before and after surgery

There were no significant differences in blood coagulation parameters among the 3 groups before surgery (all $P > 0.05$). After surgery, in contrast to the GA group, the CSEA group had significant differences in the parameter analysis of platelets and FIB (both $P < 0.05$), and the TIVA group was significantly different in relation to platelet, FIB, PT, and APTT (all $P < 0.05$). Evaluative comparisons conducted before surgery in the GA group exhibited no significant differences in any parameters after surgery (all $P > 0.05$). The CSEA group showed a decrease in platelets and an increase in APTT (both $P < 0.05$). The TIVA group had decreases in FIB and increase in APTT (both $P < 0.05$) (Table 5).

BV, PV, and D-dimer content of patients in the GA, CSEA, and TIVA groups before and after surgery

Table 6 shows the BV, PV, and D-dimer content of patients in the GA, CSEA, and TIVA groups before and after surgery. When comparing the BV, PV, and D-dimer content before surgery with those on the 1st, 3rd, 7th, and 14th days after surgery, no differences in any parameters were detected (all $P > 0.05$). An exception was the PV content of the CSEA group on the 14th day after surgery, which was evaluated as being significantly different to that before surgery ($P < 0.05$).

The incidence of DVT in patients in the GA, CSEA, and TIVA groups after surgery

In the GA group (n=63), the incidence of DVT and its complications were 15.87% and 70.00%, respectively. In the CSEA

Table 7. Comparison of incidence of DVT in patients in the GA, CSEA and TIVA groups after surgery.

Parameter	GA group	CSEA group	TIVA group
DVT			
Yes	10 (15.87%)	10 (14.93%)	3 (4.48%)
No	53 (84.13%)	57 (85.07%)	64 (95.52%)
Complications			
Yes	7 (70.00%)	7 (70.00%)	0 (0.00%)
No	3 (30.00%)	3 (30.00%)	3 (100.00%)

DVT – deep venous thrombosis; GA – general anesthesia; CSEA – combined spinal-epidural anesthesia; TIVA – total intravenous anesthesia.

Table 8. Logistic regression analysis for risk factor for the incidence of DVT.

Factor	Regression coefficient	Standard deviation	Wald	P	OR	95% CI	
						Lower limit	Upper limit
Type of anesthesia	4.316	1.512	8.153	0.004	74.917	3.871	1449.826
SBP	-0.044	0.021	4.145	0.042	0.957	0.918	0.998
DBP	0.017	0.019	0.811	0.368	1.018	0.98	1.057
RBC	0.184	0.119	2.375	0.123	1.202	0.951	1.519
WBC	-0.321	0.15	4.559	0.033	0.726	0.541	0.974
Neutrophil	0.459	0.242	3.593	0.058	1.582	0.985	2.541
Monocyte (10 ⁹ /L)	-0.692	1.72	0.162	0.688	0.501	0.014	14.568
Lymphocyte	-0.678	0.607	1.248	0.264	0.508	0.155	1.688
Swallowing reflex time	0.215	0.094	5.205	0.023	1.24	1.031	1.492
Extubation time	0.296	0.078	14.472	<0.001	1.344	1.154	1.565
Consciousness recovery time	0.518	0.163	10.125	0.001	1.679	1.22	2.31
Plt	-0.029	0.014	4.211	0.04	0.971	0.945	0.999
FIB	0.551	0.3	3.384	0.066	1.735	0.965	3.122
PT	-0.553	0.413	1.669	0.196	0.587	0.261	1.318
APTT	-0.055	0.091	0.363	0.547	0.947	0.792	1.132
Pv	-2.093	1.647	1.616	0.204	0.123	0.005	3.108

OR – odds ratio; 95% CI – 95% confidence interval; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; SPO₂ – saturation of peripheral oxygen; FIB – plasma fibrinogen; PT – prothrombin time; APTT – activated partial thromboplastin time.

group, the incidence of DVT was 14.93% and the incidence of its complications was 70.00%. In the TIVA group, the incidence of DVT and its complications were found to be 4.48% and 0.00%, respectively. There were significant differences detected in the incidence of DVT and its complications among the 3 groups (all $P < 0.05$). Moreover, the incidence of DVT and its complications were found to be lower in the TIVA group than in the GA and CSEA groups (all $P < 0.05$) (Table 7).

Logistic regression analysis for risk factor for the incidence of DVT

The incidence of DVT served as a dependent variable. The independent variables included factors that were found to be significantly different: type of anesthesia, SBP, DBP, RBC, WBC, neutrophil, monocyte, lymphocyte, swallowing reflex time, extubation time, consciousness recovery time, Plt, FIB,

PT, APTT, and P_v. Logistic regression analysis was used for further statistical analysis. The results suggested that the type of anesthesia, SBP, WBC, swallowing reflex time, extubation time, consciousness recovery time, and Plt were all independent correlative factors for the incidence of DVT (all $P < 0.05$). This indicates that the type of anesthesia used was a significant factor in relation to the incidence of DVT and DVT related complications (Table 8).

Discussion

Lower-extremity DVT poses a major and, at times, fatal complication in patients after a TKA procedure. As a result, DVT is a significant surgical risk and a dominant cause of morbidity and mortality [8,12]. More recently, it has been revealed that different anesthesia methods employed in the application of TKA result in varying degrees of implications in relation to DVT [13]. Consequently, our central objective was to explore the effects of these 3 different anesthesia methods (GA, CSEA, and TIVA) on DVT occurrence after TKA. Our results show that TIVA has the lowest risk of DVT.

Firstly, we found that the TIVA group had the lowest incidence of lower-limb DVT and DVT-related complications, followed by the CSEA group and the GA group. General anesthesia is used during surgery to allowing the patient to become totally unconscious. This requires the anesthetist to meticulously control pulse rate, intraoperative blood pressure, and, at times, even the volatile agent. In regards to TIVA application, there is an avoidance of the utilization of inhalation agents, which is done by sustaining a constant infusion of propofol and remifentanyl [18]. CSEA is a relatively new combined technique that has gained wide acceptance owing to its ability to retain the reliability of spinal anesthesia and the flexibility of epidural anesthesia, while avoiding their respective disadvantages, thus giving it a significant advantage over general anesthesia [19]. A previous study demonstrated that the use of TIVA and local anesthetics during longer, more complex cases such as an abdominoplasty could spare the patient additional risks of general anesthesia and endotracheal intubation [16]. Compared with GA, TIVA has many advantages over inhalational anesthesia, such as minimal cardiac depression, fewer neurohumoral responses, and decreased oxygen consumption, which contribute to ultimately avoiding postoperative diffusion hypoxemia and decrease the incidence of postoperative nausea and vomiting [14]. In addition, TIVA can maintain hemodynamic stability, allowing it to contribute to the prevention of lower-extremity DVT by reducing intraoperative blood loss with a dry surgical field and enhanced redistribution of blood flow to the leg muscles [20]. Epidural anesthesia is known to reduce postoperative thromboembolic complications as well as having the potential to deter the development of lower-extremity

DVT by preventing postoperative hypercoagulability without affecting physiologic aggregation and coagulation processes [21], thus making it a more effective method than GA. This result was consistent with studies conducted by Bansal et al., who found that TIVA with propofol and analgesic drugs in a simultaneous fashion without any inhaled drugs could greatly improve surgical efficacy when compared to other means of anesthesia [22]. Furthermore, Chen et al. reported similar findings in parallel with the conclusive results of this study, in regards to combined spinal-regional anesthesia being a more effective option during surgical operation than that of GA [23].

Secondly, we found that the TIVA group had decreases in FIB, reduced platelets, and increased APTT compared to the other 2 groups. FIB operates as an integral part of the hemostatic system; it is the precursor of fibrin and the end-product of blood coagulation [24]. Platelet activation is both complementary and mutually dependent on blood coagulation in hemostasis and thrombosis by interacting with several coagulation factors [25]. APTT, a global coagulation test of clotting factor levels of the intrinsic system, has been widely used to search for lupus anticoagulants, and as a test of choice for dose-adjustment [26]. Additionally, APTT reflects both the common intrinsic pathways involved in the coagulation cascade; this makes it a particularly useful marker for thrombotic activity [27]. During the development of DVT venous stasis, blood coagulation and release of thromboplastin are interrupted [28,29]. Klovaite et al. found that elevated levels of FIB promoted blood coagulation and structural properties of the thrombus, facilitating the development of lower-extremity DVT [30]. Previous reports have also indicated DVT occurrence is linked with platelet level increase [31]. Hron et al. reported that patients with higher risks for DVT had shorter APTT, while those with lower risks had notably longer APTT [32]. Considering that our study found that TIVA carries the lowest risk for developing DVT after TKA, we can confirm the results reported by Klovaite et al. and Hron et al., as they mirrored and provided much support to the findings of the present study.

Conclusions

In regards to all the content discussed above, we conclude that the 3 anesthesia methods investigated had varying degrees of influence on the development of DVT following a TKA procedure. TIVA exhibited the lowest rate of potential DVT and DVT-related complications. Therefore, our results can be of clinical use based on our evaluation of anesthesia methods in relation to TKA procedures. However, this study also has limitations. Firstly, it was based on a small sample size, which may affect the overall impact in terms of clinically convincing results. Therefore, more experiments are needed to confirm our results. Secondly, because we followed the patients for a

relatively short period of time (3 months), studies with longer follow-up are needed to verify the results obtained. Thirdly, we did not discuss the different requirements and standards in different types of anesthesia, which also might cause the difference in the incidence of DVT. Finally, the results of our study indicated that the increase of the volatile agent isoflurane may become a factor for the formation of DVT, but our study mainly explored the incidence of lower-extremity DVT in patients receiving TKA with 3 different anesthesia methods. Therefore, the effects of the volatile agent isoflurane on the

formation of DVT needs to be addressed in future studies. In summary, similar studies with larger sample sizes, spanning longer periods are needed to verify our results. This will ultimately lead to the better application of optimal anesthesia methods to further protect patients from DVT and DVT-related complications following TKA procedures.

Conflict of interests

None.

References:

1. Harvey LA, Brosseau L, Herbert RD: Continuous passive motion following total knee arthroplasty in people with arthritis. *Cochrane Database Syst Rev*, 2010; 2010: CD004260
2. Bozic KJ, Kurtz SM, Lau E et al: The epidemiology of revision total knee arthroplasty in the United States. *Clin Orthop Relat Res*, 2010; 468: 45–51
3. Rajewsky B, Werner E: [Continuous measurement of serum electrolytes in rabbits under the effect of ionizing radiation]. *Fortschr Geb Rontgenstr Nuklearmed*, 1972; Suppl: 59–60 [in German]
4. Diduch DR, Insall JN, Scott WN et al: Total knee replacement in young, active patients. Long-term follow-up and functional outcome. *J Bone Joint Surg Am*, 1997; 79: 575–82
5. Sharkey PF, Lichstein PM, Shen C et al: Why are total knee arthroplasties failing today – has anything changed after 10 years? *J Arthroplasty*, 2014; 29: 1774–78
6. Kim YH, Choi YW, Kim JS: Simultaneous bilateral sequential total knee replacement is as safe as unilateral total knee replacement. *J Bone Joint Surg Br*, 2009; 91: 64–68
7. Bourne RB, Chesworth BM, Davis AM et al: Patient satisfaction after total knee arthroplasty: Who is satisfied and who is not? *Clin Orthop Relat Res*, 2010; 468: 57–63
8. Lassen MR, Ageno W, Borris LC et al: Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med*, 2008; 358: 2776–86
9. Burnside PR, Brown MD, Kline JA: Systematic review of emergency physician-performed ultrasonography for lower-extremity deep vein thrombosis. *Acad Emerg Med*, 2008; 15: 493–98
10. Vedantham S, Thorpe PE, Cardella JF et al: Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol*, 2009; 20: S227–39
11. Sadaghianloo N, Jean-Baptiste E, Declémy S et al: Use of aspirin for the prevention of lower extremity deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord*, 2014; 2: 230–39
12. Nazir SA, Ganeshan A, Nazir S, Uberoi R: Endovascular treatment options in the management of lower limb deep venous thrombosis. *Cardiovasc Intervent Radiol*, 2009; 32: 861–76
13. Bouaziz H, Bondar A, Jochum D et al: Regional anaesthesia practice for total knee arthroplasty: French national survey – 2008. *Ann Fr Anesth Reanim*, 2010; 29: 440–51
14. Singh Bajwa SJ, Bajwa SK, Kaur J: Comparison of two drug combinations in total intravenous anesthesia: Propofol-ketamine and propofol-fentanyl. *Saudi J Anaesth*, 2010; 4: 72–79
15. Salman C, Kayacan N, Ertugrul F et al: Combined spinal-epidural anesthesia with epidural volume extension causes a higher level of block than single-shot spinal anesthesia. *Braz J Anesthesiol*, 2013; 63: 267–72
16. Failey C, Aburto J, de la Portilla HG et al: Office-based outpatient plastic surgery utilizing total intravenous anesthesia. *Aesthet Surg J*, 2013; 33: 270–74
17. Chan IA, Maslany JG, Gorman KJ et al: Dexmedetomidine during total knee arthroplasty performed under spinal anesthesia decreases opioid use: A randomized-controlled trial. *Can J Anaesth*, 2016; 63: 569–76
18. Wormald PJ, van Renen G, Perks J et al: The effect of the total intravenous anesthesia compared with inhalational anesthesia on the surgical field during endoscopic sinus surgery. *Am J Rhinol*, 2005; 19: 514–20
19. Choi DH, Kim JA, Chung IS: Comparison of combined spinal epidural anesthesia and epidural anesthesia for cesarean section. *Acta Anaesthesiol Scand*, 2000; 44: 214–19
20. Eroglu A, Uzunlar H, Erciyes N: Comparison of hypotensive epidural anesthesia and hypotensive total intravenous anesthesia on intraoperative blood loss during total hip replacement. *J Clin Anesth*, 2005; 17: 420–25
21. Hollmann MW, Wiecek KS, Smart M, Durieux ME: Epidural anesthesia prevents hypercoagulation in patients undergoing major orthopedic surgery. *Reg Anesth Pain Med*, 2001; 26: 215–22
22. Cole CD, Gottfried ON, Gupta DK, Couldwell WT: Total intravenous anesthesia: advantages for intracranial surgery. *Neurosurgery*, 2007; 61: 369–77; discussion 377–78
23. Kuzgunbay B, Turunc T, Akin S et al: Percutaneous nephrolithotomy under general versus combined spinal-epidural anesthesia. *J Endourol*, 2009; 23: 1835–38
24. Uitte de Willige S, de Visser MC, Houwing-Duistermaat JJ et al: Genetic variation in the fibrinogen gamma gene increases the risk for deep venous thrombosis by reducing plasma fibrinogen gamma' levels. *Blood*, 2005; 106: 4176–83
25. Heemskerk JW, Bevers EM, Lindhout T: Platelet activation and blood coagulation. *Thromb Haemost*, 2002; 88: 186–93
26. Tripodi A, Mannucci PM: Activated partial thromboplastin time (APTT). New indications for an old test? *J Thromb Haemost*, 2006; 4: 750–51
27. Ali A, Mohan P, Kareem H et al: Elevated factor VIII levels and shortened APTT in recurrent abortions. *J Clin Diagn Res*, 2016; 10: EC04–6
28. Goldberg A: Prevention of deep-vein thrombosis after total knee replacement. *J Bone Joint Surg Br*, 2000; 82: 304–5
29. Tuman KJ, McCarthy RJ, March RJ et al: Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg*, 1991; 73: 696–704
30. Klovaite J, Nordestgaard BG, Tybjaerg-Hansen A, Benn M: Elevated fibrinogen levels are associated with risk of pulmonary embolism, but not with deep venous thrombosis. *Am J Respir Crit Care Med*, 2013; 187: 286–93
31. Simanek R, Vormittag R, Ay C et al: High platelet count associated with venous thromboembolism in cancer patients: Results from the Vienna Cancer and Thrombosis Study (CATS). *J Thromb Haemost*, 2010; 8: 114–20
32. Hron G, Eichinger S, Weltermann A et al: Prediction of recurrent venous thromboembolism by the activated partial thromboplastin time. *J Thromb Haemost*, 2006; 4: 752–56