Effects of general and epidural anesthesia on the formation of deep vein thrombosis after total knee arthroplasty: a meta-analysis

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Abstract

BACKGROUND: Although the therapeutic effect of total knee arthroplasty for severe gonarthritis is reliable, deep vein thrombosis also occurred in many patients. Therefore, deep vein thrombosis has been a major reason for unexpected death after total knee arthroplasty.

OBJECTIVE: To study the incidence of deep vein thrombosis after total knee arthroplasty with general and epidural anesthesia.

METHODS: We searched “PubMed”, “Medline”, “Elsevier”, “Embase”, Cochrane library, “Wanfang”, “China National Knowledge Infrastructure” for papers published from January 2000 to March 2015. The mesh words were “total knee arthroplasty”, “TKA”, “thrombosis”, “DVT”, “randomized controlled trial”, “RCT” for studies concerning deep vein thrombosis after total knee arthroplasty with different anesthetic methods. The double blind method was used for data extraction and assessment of literature quality. Revman5.3 software was utilized to analyze the extracted data using meta-analysis.

RESULTS AND CONCLUSION: There were 8 studies including 885 patients. The heterogeneity of the included studies was very low (I^2=0, P=0.72). The combined OR was 0.25 (95% confidence interval: 0.18, 1.35), indicating that continuous epidural anesthesia in total knee arthroplasty could apparently reduce the possible formation of postoperative deep vein thrombosis. Because of lack of the changes in coagulation factors under general anesthesia and epidural anesthesia, the mechanism underlying epidural anesthesia to reduce the incidence of deep vein thrombosis deserves further investigations. Among patients with deep vein thrombosis, continuous epidural anesthesia could diminish the possible formation of deep vein thrombosis. Thus, epidural anesthesia should be used firstly for knee replacement in patients with high risk of deep vein thrombosis.

Subject headings: Arthroplasty, Replacement, Knee; Venous Thrombosis; Anesthesia; Anesthesia, Epidural

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INTRODUCTION

The invention of total knee arthroplasty (TKA) is one of the most significant advancements in the 20th century medicine. This technique has effectively alleviated the pain of patients with late-stage osteoarthritis, enhanced their ability of mobility, and raised the quality of their life. With the economic development and the increase in the number of elderly population, TKA has already become one of the common surgical procedures in most regional center hospitals. However, patients who underwent TKA have high risks for developing deep vein thrombosis (DVT)[1]. DVT, especially the pulmonary thromboembolism that can be caused by DVT, is a major reason of mortality in patients after the surgery[2-4]. Considering the high mortality that can be caused by DVT after TKA, how to avoid it is one of the most important factors in reducing mortality rate after TKA.

Although many studies analyze the risk factors for the formation of DVT in patients who underwent TKA, there are no randomized controlled studies including large patient samples to reach a conclusion with high evidence level. General and epidural anesthesia are the most commonly used anesthetic methods while performing TKA. Since these two methods have significantly different working mechanisms, they have different effects on the hemodynamics and blood coagulation factors during and after the surgery. We assume that choosing general or epidural anesthesia should lead to different incidences of DVT. However, there are no studies with large sample or meta-analysis to

find out if choosing general or epidural anesthesia affects the incidence of DVT after TKA. In the current study, we did a meta-analysis on current publications comparing the incidence of DVT after TKA under different anesthetic methods to come up with evidence of higher quality, and to guide clinical work in the future.

MATERIALS AND METHODS

Search strategy

Two independent reviewers underwent computerized search of databases as PubMed (2000–2015), Medline (2000–2015), Embase (2000–2015), Elsevier (2000–2014), Cochrane library (2008–2014), China National Knowledge Infrastructure (2000–2015) with the mesh words: "total knee arthroplasty", "TKA", "thrombosis", "DVT", "randomized controlled trial", "RCT". For the papers whose eligibility for the inclusion criteria failed to reach consensus between the two authors, the third author was invited to settle the disputes.

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) Study design: randomized controlled trials, half randomized controlled studies, prospective and retrospective cohort studies; (2) objective: patients who needed TKA; (3) intervention methods: TKA under general and epidural anesthesia; (4) outcome indicators: formation of DVT observed by ultrasound examinations after the surgery.

Exclusion criteria: included patients with DVT before the surgery; included patients with conditions that may easily cause DVT; papers in languages other than English and Chinese; reviews, expert opinions, lectures.

Study quality assessment

Two authors independently assessed the quality of the included studies by the 12 criteria recommended by the Cochrane Back Review Group[5]. Each study was scored by "+" (positive), "–" (negative) and "?" (unclear). In the case of disputes, the third author made the final decisions. Studies with less than six "+" were recognized as with low methodological quality and high risk of bias. The methodological quality of the included trials is outlined in **Table 3**.

Data extraction

Data in the included trails were extracted by two independent reviewers. Authors of each study, study design, patient size, patients'age, origin, time of follow up as well as intervention methods. Patient numbers with and without DVT in each study were extracted and recorded in specific tables. In the cases that the same patients were analyzed in more than one study, they were extracted and analyzed as one patient population.

Statistical analysis

Data were analyzed and processed in Review Manager 5.3 as supplied by the Cochrane Collaboration (Oxford, UK). Two authors checked the data input to make sure that no errors were made. Considering that there can be publication bias between the papers, the analyses were performed using random effect models. I^2 test was used to test the heterogeneity. Studies were considered to have significant heterogeneity if I^2 >50%. Subgroup or sensitivity analysis was used at the incidence of significant heterogeneity due to methodological quality of included trials. The differences in each study were defined by the odds ratio (*OR*) with 95% confidence intervals (95%*CI*) of the categorical outcome frequencies in the study groups and the control groups, respectively. *OR* of each individual trial was shown in a forest plot.

RESULTS

Results of study retrieval

Among the 1 086 papers screened, eight papers were chosen for the final analysis[6-13] (**Figure 1**). The meta-analysis included a total number of 885 patients, 366 of whom underwent TKA with general anesthesia, and 519 underwent TKA with epidural anesthesia (**Table 1**). Most studies were proved to be of relatively high-quality assessment according the Dephli list (**Table 2**).

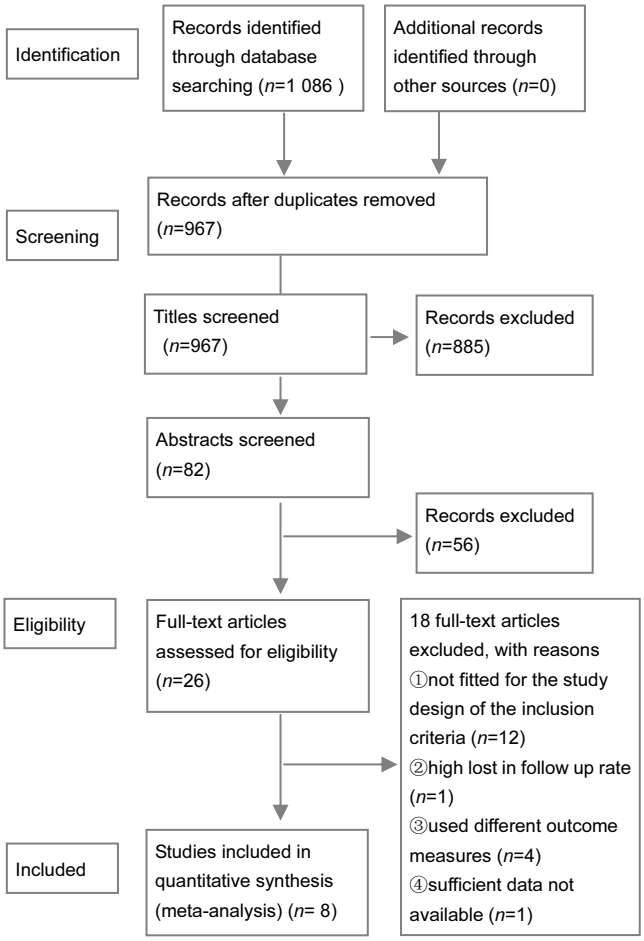

Figure 1 Diagram of the selection of papers of the current research

Meta-analysis

There were 8 studies including 885 patients concerning the incidence of DVT formation after TKA. The heterogeneity of the included studies was very low (I^2=0, *P*=0.72). However,

Table 1 Demographic characteristics of included studies

Included studies	Groups	Patient No.	Age	Study type	Time of study
Chen 2009	General	75	61.9±10.3	Retrospective	2003–2008
	Epidural	69			
Chen 2012	General	36	64.9±8.2	RCT	2009.9–2011.1
	Epidural	36	66.7±7.1		
Guo 2013	General	23	58.3(24–80)	Prospective cohort	2011.6–2012.6
	Epidural	125			
Lu 2013	General	30	53.2±3.1	RCT	2009.9–2011.1
	Epidural	30	51.9±4.2		
Song 2010	General	30	66.0±6.0	RCT	Not given
	Epidural	30	64.0±7.0		
Wu 2013	General	64	61.7±12.1	Retrospective	2008.4–2012.10
	Epidural	38			
Yan 2013	General	23	59.6±8.6	Prospective cohort	2008.2–2012.9
	Epidural	91			
Zhu 2014	General	85	65.0	Retrospective	2011.1–2012.12
	Epidural	100			

Note: RCT: Randomized controlled trial.

Table 2 The Dephli list assessing the risk of bias in all included papers

Item	Chen 2009	Chen 2012	Guo 2013	Lu 2013	Song 2010	Wu 2013	Yan 2013	Zhu 2014
Adequate Random Sequence Generation?	?	+	–	+	+	–	–	–
Adequate Allocation Concealment?	+	+	+	+	+	–	+	–
Adequate Blinding of Patients?	–	–	–	–	–	–	–	–
Adequate Blinding of Care Providers?	–	–	–	–	–	–	–	–
Adequate Blinding of Outcome Assessment?	+	+	+	+	+	+	+	+
Incomplete Outcome Data Addressed? (Loss to Follow-up)	+	+	+	+	+	+	+	+
Intention-to-Treat Analysis?	+	+	+	–	+	?	?	–
Groups Similar at Baseline?	+	+	+	+	+	+	+	+
Influence of Cointerventions Unlikely?	+	+	+	+	+	+	+	+
Adequate Compliance With Primary Intervention?	+	+	+	+	+	+	+	+
Timing of Outcome Assessments Similar?	+	+	+	+	?	+	+	+
Absence of Other Bias?	?	+	–	+	+	+	+	+
Total score	8	10	8	9	9	7	8	7

Note: +: positive; –: negative; ?: unclear.

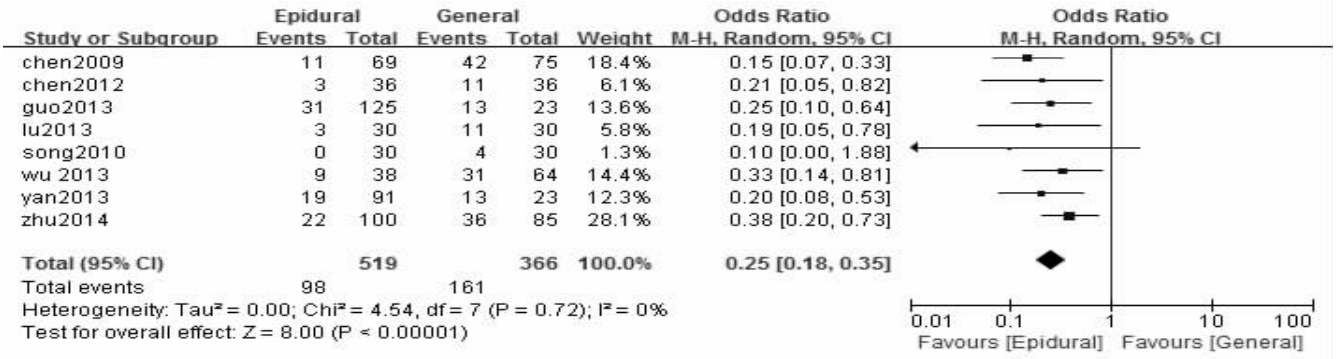

Figure 2 Comparison of the incidence of DVT after TKA with different anesthetic methods

Note: patients received epidural anesthesia had significantly lower incidence of DVT than patients received general anesthesia. DVT: deep vein thrombosis; TKA: total knee arthroplasty.

random effect model was used to compare the incidence of DVT formation after TKA. The combined *OR* was 0.25 (95% *CI*: 0.18, 1.35), indicating that patients received epidural anesthesia had significantly lower incidence of DVT than patients received general anesthesia ($P < 0.01$) (**Figure 2**).

In order to find the mechanism of this phenomenon, we compared some other factors that could affect the incidence of DVT formation after the surgery, such as duration of the surgery, intraoperative blood loss, prothrombin time (PT), plasma thromboplstin antecedent (PTA), fibrinogen (FIB), activated partial thromboplastin time (APTT) and thrombin time (TT). As a result, there were no significant differences between the two methods (**Figure 3**).

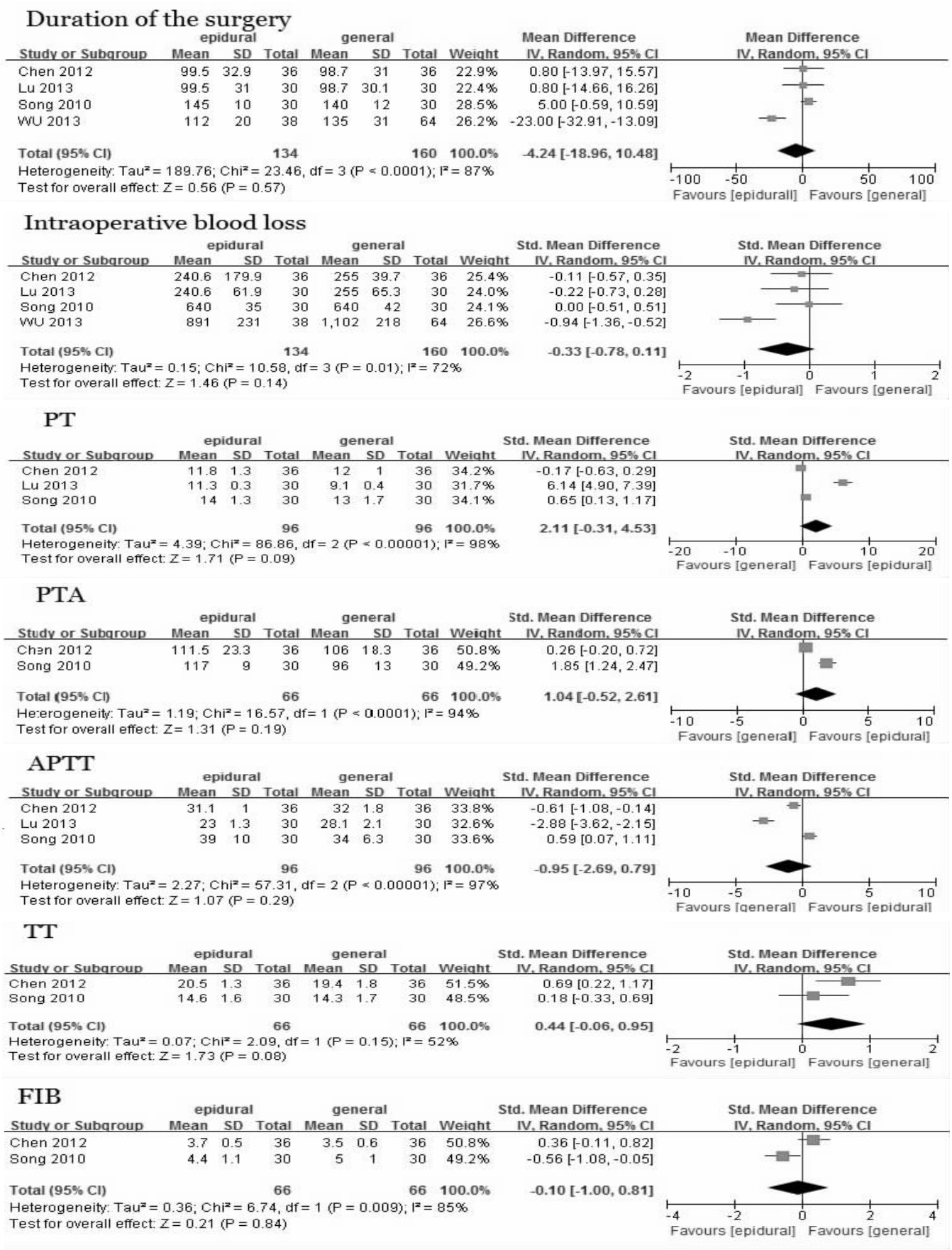

Figure 3 Comparison of factors related to the formation of DVT after TKA under different anesthetic methods

Note: there were no significant differences in duration of the surgery, intraoperative blood loss, PT, PTA, FIB, APTT and TT between the two methods. DVT: deep vein thrombosis; TKA: total knee arthroplasty; PT: prothrombin time; PTA: plasma thromboplstin antecedent; FIB: fibrinogen; APTT: activated partial thromboplastin time; TT: thrombin time.

DISCUSSION

DVT is caused by the abnormal coagulation of blood in the deep vein. DVT often appears in lower extremities, and is one of the most serious complications after TKA. In most cases, DVT could cause swelling and pain of the lower extremities, and when the thrombus moves to lung and causes pulmonary embolism, it may end up with sudden death of the patient. With the application of anticoagulation drugs, the incidence of DVT has been dropped to 42% from the original 88% without any anticoagulants. Statistically, 0.2% of those patients developed pulmonary thromboembolism and resulted in sudden death[14-15]. More than 300 thousand patients died of pulmonary thromboembolism each year[16]. The prevention of thromboembolic disease is one of the most important points in preventing mortality after TKA.

Plenty of studies concern the risk factors of DVT after TKA. According to the current literature, the high risk factors of DVT formation after TKA include old age, female, overweight and application of bone cement during the surgery[17]. In the current meta-analysis, patients with epidural anesthesia had significantly less DVT than patients who underwent TKA with general anesthesia. This result is in accordance with some other studies[18-19].

A number of reasons could be the causes of this effect. Epidural anesthesia has less effect on the blood coagulation than general anesthesia, drives more volume flow to the lower limbs and reduces the surgical stress response in the patient[20-21]. Epidural anesthesia can deactivate sympathetic nerves, dilate the blood vessels and increase the blood flow of the lower limb, decrease the secretion of catecholamine[22-23]. Moreover, patients with epidural anesthesia can walk shortly after the surgery, and then lower the incidence of DVT.

Although there were no significant differences between the two groups concerning factors that could affect the incidence of DVT formation after the surgery, such as duration of the surgery, intraoperative blood loss, PT, PTA, FIB, APTT and TT, it is possibly the bias that was caused by the sample size included in those meta-analysis.
It can be concluded from the current study that, continuous epidural anesthesia can significantly reduce the incidence of DVT if it replaces general anesthesia during TKA. This alteration should be considered in patients with high risk of forming thromboembolism such as varicose veins, malignancy, smoking, old age and the use of oral oestrogens[19]. We believe it is also possible that the incidence of DVT can be significantly lowered if general anesthesia is replaced by epidural anesthesia in patients with severe fractures of the lower extremity.

To our knowledge, the current meta-analysis is so far the study with the largest sample size. Although most of the studies included were published in Chinese language, the quality of those studies was tested by the Dephli list and proved to be qualified enough to be included in the meta-analysis. Moreover, the results driven from these studies can still serve as high grade evidence that can guide future clinical practice.

Results of this meta-analysis reveal that the ratio of DVT formation can be significantly ($P < 0.01$) reduced if general anesthesia can be replaced by epidural anesthesia in patients undergoing TKA.

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不同麻醉方式对膝关节置换后下肢静脉血栓形成的影响：Meta 分析

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文章亮点：

1 目前虽然有较大量的研究在探讨膝关节置换后下肢静脉血栓形成的危险因素以及其预防方法，但是不同麻醉方式对下肢静脉血栓形成的影响方面只有零星的小规模研究，没有大规模随机对照研究，更没有一个包含大量病例的 Meta 分析研究。

2 文章是目前所发表的包含病例数量最多探讨不同麻醉方式对全膝关节置换后下肢静脉血栓形成影响的 Meta 分析研究，且纳入本文的文献质量相对较高，文献之间的异质性低，结果可靠，能为未来的临床实践提供较可靠的循证医学依据。

关键词：
植入物；人工假体；膝关节置换；下肢静脉血栓形成；全身麻醉；硬膜外麻醉；Meta 分析
主题词：
关节成形术，置换，膝；静脉血栓形成；麻醉；麻醉，硬膜外

摘要

背景：虽然全膝关节置换治疗严重膝关节炎患者疗效可靠，但是，下肢静脉血栓形成仍会在很多患者中发生，因此下肢静脉血栓形成也成了目前接受全膝关节置换后突然死亡的最主要原因。

目的：比较不同麻醉方式下进行全膝关节置换后下肢静脉血栓形成的差异。

方法：利用“total knee arthroplasty”，“TKA”，“thrombosis”，“DVT”，“randomized controlled trial”，“RCT”，“全膝关节置换”“血栓”“麻醉”等关键词在“PubMed”，“Medline”，“Elsevier”，“Embase”，“Cochrane library”，“万方”，“CNKI”等国内外主要数据库搜集了 2000 年 1 月到 2015 年 3 月期间发表的涉及到不同麻醉方式对膝关节置换后下肢深静脉血栓形成的影响方面的文献资料。通过双盲法进行数据提取，文献质量评估，并利用 Revman5.3 统计软件对所提取的数据进行了 meta 分析。

结果与结论：最后总共有包含 885 例患者的 8 个文献被纳入此研究。通过分析发现在纳入的文献之间不存在显著异质性(I^2=0，P=0.72)。数据合成后的 *OR* 是 0.25(95% *CI:* 0.18, 1.35)，说明利用连续硬膜外麻醉方式进行全膝关节置换能显著降低术后深静脉血栓形成的可能。因为缺乏全身麻醉与硬膜外麻醉下的患者凝血因子变化情况等数据，硬膜外麻醉降低深静脉血栓发生率的机制尚需进一步研究。说明在接受下肢静脉血栓的患者中，利用连续硬膜外麻醉可显著降低下肢静脉血栓的形成可能。因此在下肢静脉血栓形成高危患者中应该优先使用硬膜外麻醉方式进行膝关节置换。

作者贡献：第一作者负责论文撰写，第一、二作者负责通过盲法独立进行资料整理，数据提出与计算。文献分析时第一、二作者出现意见不统一，第三、四、五作者评估做出最后决定。

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学术术语：硬膜外麻醉-将局麻药注入硬膜外腔，阻滞脊神经根，暂时使其支配区域产生麻痹。根据给药的方式可分为单次法和连续法。根据穿刺部位可分为高位、中位、低位及骶管阻滞。

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