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Spinal anesthesia increases the risk of venous thromboembolism in total arthroplasty

Secondary analysis of a J-PSVT cohort study on anesthesia

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Abstract

Clinical guidance on the choice of anesthetic modality vis-à-vis the risk of perioperative venous thromboembolism (VTE) is largely lacking because of a paucity of recent evidence. A comparative effect of general anesthesia and neuraxial blockade on the perioperative incidence of VTE has not been well-investigated.

We compared the effects of different types of anesthetic modalities on the risk of VTE after total hip arthroplasty (THA) and total knee arthroplasty (TKA).

This is a secondary analysis of the Japanese Study of Prevention and Actual Situation of Venous Thromboembolism after Total Arthroplasty (J-PSVT). Data pertaining to a total of 2162 patients who underwent THA and TKA at 34 hospitals were included in this analysis. We compared the different anesthetic modalities with respect to the incidence of VTE. The composite end-point was asymptomatic/symptomatic deep vein thrombosis detected using scheduled bilateral ultrasonography up to postoperative day (POD) 10 and fatal/non-fatal pulmonary embolism up to POD 10.

The study groups were as follows: general anesthesia (n = 646), combined epidural/general anesthesia (n = 1004), epidural anesthesia (n = 87), and spinal anesthesia (n = 425). On multivariate analysis, only spinal anesthesia was associated with a significant increase in the risk of VTE as compared with that associated with general anesthesia. Propensity score-matched analysis for "combined epidural/general anesthesia group" versus "spinal anesthesia group" demonstrated a 48% higher incidence of VTE (relative risk = 1.48, 95% confidence interval [CI] 1.18–1.85) in the latter.

Spinal anesthesia was associated with a higher risk of postoperative VTE, as compared with that associated with combined epidural/general anesthesia, in patients undergoing total arthroplasty.

Abbreviations: CI = confidence interval, CUS = compression ultrasonography, DVT = deep vein thrombosis, J-PSVT = the Japanese Study of Prevention and Actual Situation of Venous Thromboembolism after Total Arthroplasty, NHO = National Hospital Organization, OR = odds ratio, PE = pulmonary embolism, POD = postoperative day, THA = total hip arthroplasty, TKA = total knee arthroplasty, VTE = venous thromboembolism.

Keywords: arthroplasty, epidural anesthesia, general anesthesia, spinal anesthesia, venous thromboembolism

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1. Introduction

The association between venous thromboembolism (VTE) prophylaxis and anesthesia during orthopedic surgery has been well known for a long time. The association between the type of anesthesia and the risk of postoperative VTE is well documented. Vasodilation occurring during general anesthesia contributes to the onset of VTE by causing venous stasis, increase in venous capacitance, and decrease in venous return.[1] Use of neuraxial blockade in orthopedic procedures has been shown to be safer in this respect with a low risk of VTE, intraoperative bleeding, length of hospital stay, and risk of surgical site infection.[2,3] However, the advantage of neuraxial blockade with respect to VTE may no longer be relevant because of advances made in general anesthesia and pharmacological and mechanical thromboprophylaxis.[4,5] Furthermore, extended neuraxial blockade, such as that required for epidural analgesia, may delay the initiation of postsurgical pharmacological prophylaxis owing to the associated risk of spinal and/or epidural hematoma, possibly leading to a permanent neurological deficit, such as paraplegia.[6] There are no specific clinical guidelines for the choice of anesthesia, largely because of insufficient recent evidence from studies comparing general anesthesia and neuraxial blocks for their association with VTE.

Combined epidural/general anesthesia reduces blood loss and dosage requirement for anesthetic medication, is more effective in pain control, and causes fewer postoperative complications.[7,8] Therefore, this anesthetic procedure has been widely used in orthopedic surgery for decades.[9] The Japanese Study of Prevention and Actual Situation of Venous Thromboembolism after Total Arthroplasty (J-PSVT) is a multicenter, collaborative, prospective, observational study that investigates the efficacy and safety of VTE prophylaxis after joint replacement surgery, across 34 Japanese National Hospital Organization (NHO) hospitals. In the present study, we compared the effects of different types of anesthetic modalities on the incidence of VTE in patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA).

2. Methods

This was a secondary analysis of J-PSVT, a hospital-based, non-interventional, cohort study to assess the efficacy and safety of current practices for thromboprophylaxis. The design and main results of J-PSVT have been previously reported.[10] Patients aged >20 years who were scheduled for THA or TKA for primary joint disease were eligible for inclusion. Data were collected from all patients undergoing primary THA and TKA between 2007 and 2010 in 34 NHO hospitals. The trial was registered in the Japan UMIN Clinical Trial Registry (UMIN000001366), and the study protocol was approved by the ethics committee of the NHO central institutional review board (No 0623004). Written informed consent was obtained from all patients prior to the use of their clinical records.

The study endpoint, which was a composite of asymptomatic/symptomatic deep vein thrombosis (DVT) up to postoperative day (POD) 10 and fatal/non-fatal pulmonary embolism (PE) up to POD 10, was compared with different types of anesthetic modalities.

All patients were assessed for DVT in the proximal and distal veins on POD 10 using standard compression ultrasonography (CUS). All sonographers were adequately trained. Just prior to the start of study, the sonographers received detailed instructions for standardized procedures in a specially organized conference herein they acquired the necessary certification. Symptomatic DVT and PE was diagnosed using CUS, contrast computed tomography, and lung perfusion scan.

Data on patient demographics, primary diagnosis, pre-existing comorbid conditions, length of operation, anesthesia type, and VTE prophylaxis were gathered using standard case report forms.

2.1. Statistical analysis

Discrete variables were compared using the chi-squared test; continuous variables were compared using Kruskal–Wallis rank test. Multiple logistic regression analysis was performed to identify the independent predictors of VTE. Variables with a P value of $<.2$ on univariate logistic regression analysis were included in a multivariate logistic regression model with stepwise forward selection, with forced entry of sex, surgery type, and each pharmacological prophylactic drug. These have been identified as risk factors for VTE in previous studies.[4] Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as an approximation of the relative risk of VTE with different types of anesthetic modalities, taking general anesthesia as reference.

Propensity-score matching was performed to minimize the effects of confounding caused by non-randomized assignment to the type of anesthetic modalities. This was done to reduce the impact of selection bias and allow relevant variables to be evenly balanced in the combined epidural/general and spinal anesthesia groups. Tourniquet use was strongly associated with TKA because it was used in almost all patients undergoing TKA. Therefore, all variables except tourniquet use were included in the multiple logistic regression model to estimate the propensity score, which represents the probability of the use of either combined epidural/general or spinal anesthesia. A Markov chain Monte Carlo procedure was used for multiple imputation of missing values for numerical variables, such as body mass index and estimated glomerular filtration rate. A mode imputation procedure was used to impute missing values for categorical variables such as comorbidities. The multiple and mode imputation were performed using the XLSTATBase 2015 (Addinsoft, Paris, France). Patients undergoing combined epidural/general or spinal anesthesia were matched on a 1:1 basis using nearest-number matching using a caliper of 0.01. After matching, the incidence of postsurgical VTE was compared using the chi-squared test.

All reported P values are two-tailed. Data processing and analyses were performed using the Statistical Analysis System and IBM SPSS Statistics version 23.0 for Windows (SPSS, Chicago, IL).

3. Results

In total, 2186 patients met the inclusion criteria and were enrolled in the J-PSVT study. Primary effectiveness outcome was not assessed in 24 patients owing to the lack of ultrasonography or a preoperative history of antiplatelet therapy. Thus, the study population of this subgroup study consisted of 2162 patients. Based on the type of anesthesia, they were classified into the following groups: general anesthesia (n=646), combined epidural/general anesthesia (n=1004), epidural anesthesia (n=87), and spinal anesthesia (n=425) groups. The demographics and clinical characteristics of these patients are shown in Table 1.

The incidence of VTE in the four groups was as follows: general anesthesia, 16.3%; combined epidural/general anesthesia, 17.3%; epidural anesthesia, 10.3%; and spinal anesthesia,

Table 1

Baseline characteristics of the study group patients.

	GA n=646	CEG n=1004	EA n=87	SA n=425	*P*	Missing data
Patient demographics						
Age ≥75 y	44.0 (284)	39.9 (401)	28.7 (25)	51.5 (219)	<.001	0
Sex, female	84.2 (544)	83.4 (837)	90.8 (79)	83.1 (353)	.316	0
Body mass index ≥30 kg/m^2	10.2 (66)	8.9 (89)	10.3 (9)	9.7 (41)	.812	5
Surgery						
Total knee arthroplasty	56.7 (366)	53.3 (535)	64.4 (56)	79.3 (337)	<.001	0
Operation time ≥120 min	44.3 (286)	61.9 (621)	57.5 (50)	39.3 (167)	<.001	0
Tourniquet use	54.8 (354)	50.3 (505)	64.4 (56)	22.6 (329)	<.001	0
Patient comorbidities						
History of VTE	14 (9)	0.9 (9)	1.1 (1)	0.5 (2)	.891	0
Atrial fibrillation	3.7 (21)	1.4 (11)	1.6 (1)	1.3 (5)	.020	396
Dyslipidemia	14.3 (87)	16.8 (152)	15.3 (13)	11.9 (50)	.128	141
Diabetes mellitus	14.1 (86)	12.4 (113)	10.6 (9)	13.1 (55)	.726	138
Hypertension	61.3 (345)	52.9 (406)	73.8 (45)	57.6 (217)	.001	394
Malignant tumor	5.0 (32)	4.4 (44)	3.4 (3)	5.9 (25)	.604	0
Rheumatoid arthritis	9.1 (59)	10.4 (104)	28.7 (25)	16.0 (68)	<.001	0
Initial laboratory values						
White cell count ≥10 × 10^9/L	2.2 (14)	2.2 (22)	12.6 (11)	4.2 (18)	<.001	0
Abnormal platelet number	3.9 (25)	4.2 (42)	11.5 (10)	5.9 (25)	.008	0
Serum albumin <3.5 g/dL	11.0 (71)	11.0 (110)	28.7 (25)	26.4 (112)	<.001	0
eGFR <60 mL/min/1.73 m^2	19.09 (122)	20.6 (206)	16.1 (14)	25.4 (108)	.047	5
Thromboprophylaxis after surgery						
Elastic stockings	76.5 (494)	96.4 (968)	88.5 (77)	85.2 (362)	<.001	0
Foot pump	76.6 (495)	74.6 (749)	71.3 (62)	79.8 (339)	.133	0
Unfractionated heparin	3.7 (24)	7.6 (76)	3.4 (3)	0.2 (1)	<.001	0
Enoxaparin	16.6 (107)	20.4 (205)	6.9 (6)	12.5 (53)	<.001	0
Fondaparinux	27.6 (178)	24.9 (250)	63.2 (55)	32.5 (138)	<.001	0
Warfarin	0 (0)	0 (0)	0 (0)	0 (0)	NA	0
Antiplatelets	3.1 (20)	5.4 (54)	0 (0)	3.5 (15)	.20	0

Data presented as % (n). Tourniquet was used in most patients with total knee arthroplasty and few patients with total hip arthroplasty. Therefore, data in patients with tourniquet undergoing THA were not included in the analysis. The number of patients who lacked a variable is listed in the "Missing data" column. CEG=combined epidural/general anesthesia, EA=epidural anesthesia, eGFR=estimated glomerular filtration rate, GA=general anesthesia, SA=spinal anesthesia, VTE=venous thromboembolism.

30.8% (Fig. 1). There was a significant difference in the incidence of VTE between these 4 groups ($P<.001$).

On multivariate analysis, only spinal anesthesia was significantly associated with an increased risk of VTE when compared with general anesthesia. Female sex, older age, and TKA were associated with increased VTE rates, which is consistent with an earlier report.[4] Hypoalbuminemia and fondaparinux therapy was associated with a reduced incidence of VTE (Table 2).

Finally, we directly compared combined epidural/general anesthesia and spinal anesthesia using propensity-score matching

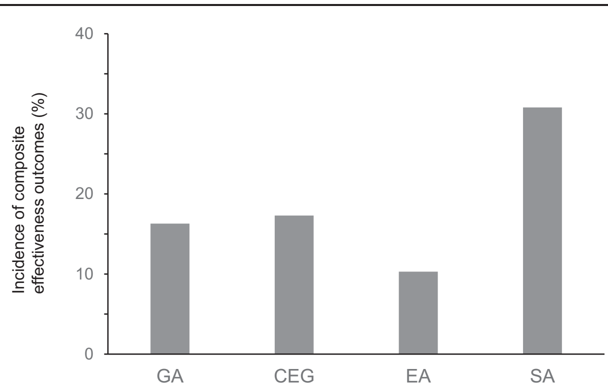

Figure 1. Incidence of venous thromboembolism in patients receiving different types of anesthetic modalities. Composite effectiveness outcomes were the results of asymptomatic/symptomatic deep vein thrombosis up to postoperative day 10 and fatal/non-fatal pulmonary embolism up to postoperative day 10. There was a significant difference in the incidence of venous thromboembolism between these 4 groups ($P<.001$). CEG=combined epidural/general anesthesia, EA=epidural anesthesia, GA=general anesthesia, SA=spinal anesthesia.

Table 2

Results of multivariate logistic regression analysis for composite effective outcomes.

Variables	Odds ratio	95% CI
Age ≥75 y	1.39	1.09–1.76
Sex, female	1.79	1.27–2.51
History of venous thromboembolism	1.51	0.73–3.12
Rheumatoid arthritis	1.14	0.80–1.62
Body mass index ≥30 kg/m^2	0.85	0.58–1.26
Operation time ≥120 min	0.86	0.68–1.08
Serum albumin <3.5 mg/dL	0.49	0.34–0.70
e-GFR <60 mL/min/1.73 m^2	1.02	0.78–1.34
Medications		
Unfractionated heparin	1.55	0.96–2.52
Enoxaparin	1.05	0.77–1.44
Fondaparinux	0.52	0.39–0.70
Antiplatelet	1.13	0.65–1.94
Total knee arthroplasty	1.95	1.50–2.54
Types of anesthetic modalities		
GA	1.00	–
CEG	1.09	0.83–1.44
EA	0.82	0.39–1.73
SA	2.39	1.75–3.26

Variable tourniquet use was not included in multivariate logistic regression because it was used in most patients with total knee arthroplasty and few patients with total hip arthroplasty. GA is the reference category for odds ratios for different types of anesthesia. CEG=combined epidural/general anesthesia, CI=confidence interval, EA=epidural anesthesia, eGFR=estimated glomerular filtration rate, GA=general anesthesia, SA=spinal anesthesia, CI=confidence interval.

Table 3

Baseline characteristics of propensity score-matched patients with combined epidural/general anesthesia and spinal anesthesia groups.

	CEG n=305	SA n=305	P
Patient demographics			
Age ≥75 y	47.2 (144)	49.8 (152)	.517
Sex, female	83.3 (254)	83.9 (256)	.827
Body mass index ≥30 kg/m^2	12.1 (37)	9.8 (30)	.365
Surgery			
Total knee arthroplasty	71.5 (218)	72.8 (222)	.718
Operation time ≥120 min	46.6 (142)	42.6 (130)	.328
Comorbidity			
History of VTE	2.0 (6)	2.0 (6)	1.000
Atrial fibrillation	1.0 (3)	1.6 (5)	.725
Dyslipidemia	12.8 (39)	12.5 (38)	.903
Hypertension	63.0 (192)	63.0 (192)	1.000
Diabetes mellitus	14.8 (45)	12.8 (39)	.481
Malignant tumor	5.9 (18)	6.2 (19)	.865
Rheumatoid arthritis	12.8 (39)	14.8 (45)	.481
Initial laboratory values			
White cell count ≥10 × 10^9/L	2.3 (7)	3.6 (11)	.474
Abnormal platelet counts	4.3 (13)	4.9 (15)	.699
Serum albumin <3.5 g/dL	18.7 (57)	21.3 (65)	.418
eGFR <60 mL/min/1.73 m^2	22.3 (68)	21.6 (66)	.845
Postoperative thromboprophylaxis			
Elastic stockings	83.56 (255)	80.7 (246)	.341
Intermittent pneumatic compression	84.9 (259)	81.6 (249)	.278
Unfractionated heparin	0 (0)	0.3 (1)	1.000
Low molecular weighted heparin	11.0 (36)	12.5 (38)	.804
Fondaparinux	40.7 (124)	37.0 (113)	.361
Antiplatelets	3.0 (9)	3.3 (10)	1.000

Data are presented as % (n). All presented variables were included in the logistic regression model for the estimation of propensity scores. CEG=combined epidural/general anesthesia, eGFR=estimated glomerular filtration rate, SA=spinal anesthesia, VTE=venous thromboembolism.

to minimize the confounding effects caused by non-randomized assignment to the type of anesthetic modalities. Concomitant liver and renal dysfunction and the use of antithrombotics may influence the choice in favor of neuraxial blockade. For this reason, the comparison of general anesthesia with spinal anesthesia is likely to be biased. Comparison of combined epidural/general anesthesia versus spinal anesthesia is likely to have eliminated this bias in our cohort. Moreover, the use of combined epidural/general anesthesia was the most frequent, whereas epidural anesthesia was the least frequent, in our cohort.

Propensity score matching allowed relevant variables to be balanced between the combined epidural/general anesthesia and spinal anesthesia groups, reducing the impact of selection bias. After propensity score matching, there were 305 patients in each group (Table 3).

In this study, spinal anesthesia increased VTE incidence by 48% (relative risk: 1.48, 95% CI, 1.18–1.85) when compared with that by combined epidural/general anesthesia (Fig. 2).

4. Discussion

In this study, spinal anesthesia was significantly associated with an increased risk of VTE in patients undergoing arthroplasty. On the other hand, VTE incidence did not differ between general anesthesia and combined epidural/general anesthesia. Although epidural anesthesia demonstrated a tendency for decreased VTE risk, this was not statistically significant owing to the relatively small sample size.

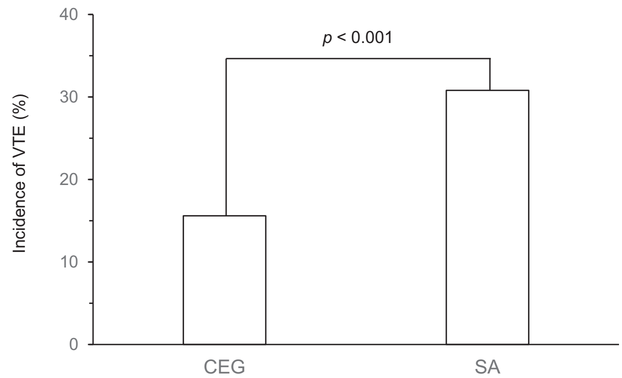

Figure 2. Incidence of venous thromboembolism among propensity-matched patients with combined epidural/general anesthesia and spinal anesthesia. White columns indicate the incidence of venous thromboembolism. There was a significant difference in the incidence of venous thromboembolism between 305 pairs of patients with combined epidural/general anesthesia and spinal anesthesia ($P < .001$). CEG=combined epidural/general anesthesia; SA= spinal anesthesia; VTE=venous thromboembolism.

Neuraxial blockade is associated with a lower risk of VTE as compared with that associated with general anesthesia.[11,12] Rheological changes in the hyperkinetic blood flow in the lower limbs may explain this effect. In addition, epidural anesthesia exerts a profibrinolytic action.[13,14] Despite the good sensorimotor blockade, spinal anesthesia is associated with a higher incidence of hypotension.[15,16] Majority of previous studies have compared epidural with general anesthesia; comparison between spinal and general anesthesia from the perspective of thromboprophylaxis in orthopedic surgery is not well-characterized.[11,12,17] However, neuraxial blockade has little advantage when perioperative heparin prophylaxis is used.[18–20] Indeed, pharmacological VTE prophylaxis is a standard component of the protocol of care for orthopedic patients.[5]

Conversely, epidural anesthesia added to general anesthesia has some advantages over general anesthesia, such as reduction in blood loss and the requirement for anesthetic medication.[8] Moreover, combined epidural/general anesthesia markedly enhances venous flow in the leg because of its sympatholytic action; thus, minimizing perioperative venous stasis.[21]

However, neuraxial blockade, including spinal anesthesia, has not been compared with combined epidural/general anesthesia. Therefore, the mechanisms responsible for the effects of spinal anesthesia on postoperative thromboembolic events, relative to combined epidural/general anesthesia are unclear.

One reason for a high VTE incidence in patients with spinal anesthesia compared with those with epidural analgesia is the superior pain relief afforded by epidural analgesia, which facilitates the early postoperative mobilization of patients.[22] The neuroendocrine response to clinical stress and/or surgery is associated with increased hemostasis.[23] Other reasons may be that spinal anesthesia produces stronger freezing in the leg as compared with that by combined epidural/general anesthesia, whereas the outcome may vary according to the anesthetic agent used in epidural anesthesia.[24] However, from a hematological perspective, there were no differences in perioperative hemostatic markers between general and spinal anesthesia.[19] Continuous epidural analgesia in the postoperative recovery period attenuated some markers of hypercoagulability.[25]

Our study has several limitations. First, we consider DVT for lower leg to be an unsuitable endpoint for multicenter studies owing to the limitation of large inter-observer differences. Second, detailed information on some anesthesia-related parameters such as, level of postoperative analgesia and the timing of epidural catheter removal was not included in the analysis. Third, we did not include data on in–out balance (blood/solution infusion vs. discharge volume), blood pressure, and cardiac output during anesthesia.

Despite these limitations, our data may provide useful information on the choice of anesthesia. Surgeons who perform THA and TKA for patients at high VTE risk may consider avoiding spinal anesthesia, although careful risk and benefit assessment of spinal anesthesia should be conducted. Further studies, such as randomized controlled trials, are warranted to confirm our results.

In conclusion, our study suggests that spinal anesthesia may be associated with an increased risk of postoperative VTE, as compared with that associated with combined epidural/general anesthesia, in patients undergoing THA and TKA.

References

[1] McKenzie PJ. Deep venous thrombosis and anaesthesia. Br J Anaesth 1991;66:4–7.

[2] Sharrock NE, Haas SB, Hargett MJ, et al. Effects of epidural anesthesia on the incidence of deep-vein thrombosis after total knee arthroplasty. J Bone Joint Surg Am 1991;73:502–6.

[3] Nielsen PT, Jørgensen LN, Albrecht-Beste E, et al. Lower thrombosis risk with epidural blockade in knee arthroplasty. Acta Orthop Scand 1990;61:29–31.

[4] Falck-Ytter Y, Francis CW, Johanson NA, et al. American College of Chest Physicians. Prevention of VTE in orthopedic surgery patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of chest physicians evidence-based clinical practice guidelines. Chest 2012;141:e278S–325S.

[5] Farfan M, Bautista M, Bonilla G, et al. Worldwide adherence to ACCP guidelines for thromboprophylaxis after major orthopedic surgery: A systematic review of the literature and meta-analysis. Thromb Res 2016;141:163–70.

[6] Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med 2015;40:182–212.

[7] Khajavi MR, Asadian MA, Imani F, et al. General anesthesia versus combined epidural/general anesthesia for elective lumbar spine disc surgery: A randomized clinical trial comparing the impact of the two methods upon the outcome variables. Surg Neurol Int 2013;4:105.

[8] Ezhevskaya AA, Mlyavykh SG, Anderson DG. Effects of continuous epidural anesthesia and postoperative epidural analgesia on pain management and stress response in patients undergoing major spinal surgery. Spine (Phila Pa 1976) 2013;38:1324–30.

[9] Williams BA, Kentor ML, Williams JP, et al. Process analysis in outpatient knee surgery: effects of regional and general anesthesia on anesthesia-controlled time. Anesthesiology 2000;93:529–38.

[10] Migita K, Bito S, Nakamura M, et al. Venous thromboembolism after total joint arthroplasty: results from a Japanese multicenter cohort study. Arthritis Res Ther 2014;16:R154.

[11] Macfarlane AJ, Prasad GA, Chan VW, et al. Does regional anaesthesia improve outcome after total hip arthroplasty? A systematic review. Br J Anaesth 2009;103:335–45.

[12] Macfarlane AJ, Prasad GA, Chan VW, et al. Does regional anesthesia improve outcome after total knee arthroplasty? Clin Orthop Relat Res 2009;467:2379–402.

[13] Siau C, Ng HP, Tan GM, et al. In vitro effects of local anaesthetics on the thromboelastographic profile of parturients. Br J Anaesth 2005;94:117–20.

[14] Hahnenkamp K, Theilmeier G, Van Aken HK, et al. The effects of local anesthetics on perioperative coagulation, inflammation and microcirculation. Anesth Analg 2002;94:1441–7.

[15] Ng K, Parsons J, Cyna AM, et al. Spinal versus epidural anaesthesia for caesarean section. Cochrane Database Syst Rev 2004;2:CD003765.

[16] Pugely AJ, Martin CT, Gao Y, et al. Differences in short-term complications between spinal and general anesthesia for primary total knee arthroplasty. J Bone Joint Surg Am 2013;95:193–9.

[17] Hu S, Zhang ZY, Hua YQ, et al. A comparison of regional and general anaesthesia for total replacement of the hip or knee: a meta-analysis. J Bone Joint Surg Br 2009;91:935–42.

[18] Hole A, Terjesen T, Breivik H. Epidural versus general anaesthesia for total hip arthroplasty in elderly patients. Acta Anaesthesiol Scand 1980;24:279–87.

[19] Brueckner S, Reinke U, Roth-Isigkeit A, et al. Comparison of general and spinal anesthesia and their influence on hemostatic markers in patients undergoing total hip arthroplasty. J Clin Anesth 2003;15:433–40.

[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;17:420–5.

[21] Delis KT, Knaggs AL, Mason P, et al. Effects of epidural-and-general anesthesia combined versus general anesthesia alone on the venous hemodynamics of the lower limb. A randomized study. Thromb Haemost 2004;92:1003–11.

[22] Foss NB, Kristensen MT, Kristensen BB, et al. Effect of postoperative epidural analgesia on rehabilitation and pain after hip fracture surgery: A randomized, double-blind, placebo-controlled trial. Anesthesiology 2005;102:1197–204.

[23] 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.

[24] Ginz HF, Zorzato F, Iaizzo PA, et al. Effect of three anaesthetic techniques on isometric skeletal muscle strength. Br J Anaesth 2004;92:367–72.

[25] de la Fuente Tornero E, Garutti Martínez I, Gutiérrez Tonal B, et al. Comparison of hemostatic markers under different techniques for anesthesia-analgesia in total hip or knee replacement. Rev Esp Anestesiol Reanim 2010;57:333–40.