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SURVEY (SYSTEMATIC REVIEW)

Does Regional Anesthesia Improve Outcome After Total Knee Arthroplasty?

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Abstract Total knee arthroplasty (TKA) is amenable to various regional anesthesia techniques that may improve patient outcome. We sought to answer whether regional anesthesia decreased mortality, cardiovascular morbidity, deep venous thrombosis and pulmonary embolism, blood loss, duration of surgery, pain, opioid-related adverse effects, cognitive defects, and length of stay. We also questioned whether regional anesthesia improved rehabilitation. To do so, we performed a systematic review of the contemporary literature comparing general anesthesia and/or systemic analgesia with regional anesthesia and/or regional analgesia for TKA. To reflect contemporary surgical and anesthetic practice, only randomized, controlled trials from 1990 onward were included. We identified 28 studies involving 1538 patients. There was insufficient evidence from randomized, controlled trials alone to conclude if anesthetic technique influenced mortality, cardiovascular morbidity other than postoperative hypotension, or the incidence of deep venous thrombosis and pulmonary embolism when using thromboprophylaxis. Our review suggests there was no difference in perioperative blood loss or duration of surgery in patients who received general anesthesia versus regional anesthesia. Compared with general anesthesia and/or systemic analgesia, regional anesthesia and/or analgesia reduced postoperative pain, morphine consumption, and opioid-related adverse effects. Length of stay may be reduced and rehabilitation facilitated for patients undergoing regional anesthesia and analgesia for TKA.
Level of Evidence: Level II, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

Introduction

Total knee arthroplasty is amenable to various regional anesthesia (RA) techniques. Central neuraxial blockade (CNB) can provide excellent intraoperative anesthesia and prolonged postoperative analgesia. Peripheral nerve blockade (PNB) avoids many of the unwanted adverse effects of CNB and allows for targeted analgesia of the operative limb [17, 23, 85]. In recent years, the use of continuous PNB (CPNB) has escalated, because it has the advantage of prolonging postoperative analgesia compared with single-injection techniques [10, 33].

Despite a low rate of complications and published benefits in certain orthopaedic procedures, including superior postoperative analgesia, improved rehabilitation, and reduced length of hospital stay, there are disadvantages of RA [3–5, 12–14, 20, 58, 74, 80, 82]. There is an inherent block failure rate (reportedly between 0% and 67%), although this varies considerably with the particular block, operator experience, and method of nerve localization [19, 20, 62]. Operating room delays and a perceived risk of increased liability also are criticisms often directed at RA [46, 65]. Other limiting factors include the training required to develop the necessary technical skills for successful RA and, more recently, the expense of ultrasound

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equipment as this method of nerve localization increases in popularity. Finally, many patients are fearful of RA and may have misconceptions about the technique [53].

Although RA is undergoing a renaissance, the results of meta-analyses and randomized, controlled trials (RCTs) comparing general anesthesia (GA) and RA for major lower limb orthopaedic surgery often are conflicting [9, 15, 54, 67, 78, 84]. It is not uncommon for the results of large RCTs to disagree with each other and with those of meta-analyses [24, 31]. This latter effect can be the result of the inclusion of small studies, publication bias, sample heterogeneity between different trial populations, and meta-analysis bias [34, 49, 55]. More importantly, many trials included in recent meta-analyses were originally published more than 30 years ago and do not reflect modern anesthetic or surgical practice. During the past two decades, postoperative care of surgical patients has improved, new thromboembolic prophylaxis regimes have been introduced, and RA has advanced as a result of enhanced needle technology, block placement techniques, catheter design, and infusion pumps [26, 29, 71, 75].

We therefore performed a systematic review of the contemporary literature (published from 1990 onward) to ascertain if RA and/or regional analgesia were superior to GA and/or systemic analgesia for TKA. The specific questions we sought to answer were whether, when compared with GA and/or systemic analgesia, RA and/or regional analgesia for TKA decreased (1) mortality, (2) cardiovascular morbidity, (3) deep venous thrombosis (DVT) and pulmonary embolism (PE), (4) blood loss, (5) duration of surgery, (6) pain, (7) opioid-related adverse effects, (8) cognitive defects, and (9) length of stay. We also examined whether RA improved rehabilitation compared with GA.

Materials and Methods

We (GAP, RB) searched the electronic databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Clinical Trials (from January 1990 to October 2008) using the following population search terms: "total knee replacement" OR "total knee arthroplasty" OR "knee operation". These search results then were combined with "anesthesia" OR "analgesia" using the Boolean search operator AND. Only RCTs were included, and the search subsequently was limited to English language studies involving human adults. Each abstract then was screened to identify studies that had randomized patients to compare GA versus RA for surgery. RCTs comparing systemic versus regional techniques for postoperative analgesia also were included. The references of the resulting RCTs were examined for any relevant articles not identified in our original search. The specific outcomes sought in each article were (1) mortality, (2) cardiovascular morbidity (myocardial infarction, pulmonary edema, hypotension), (3) DVT, (4) PE, (5) blood loss, (6) duration of surgery, (7) pain (pain scores and morphine consumption), (8) opioid-related adverse effects (nausea, vomiting, pruritis, sedation, urinary retention), (9) cognitive defects, (10) length of stay, and (11) rehabilitation (knee flexion, extension, ambulation). It was noted whether each outcome was primary or secondary.

We excluded studies if surgery other than a joint arthroplasty was performed or if the knee and hip arthroplasties were treated as one study population and data for the patients undergoing knee surgery were not presented separately in the results [11, 27, 30, 81]. Studies using opioid only neuraxial techniques or in which regional analgesia was not administered on the day of surgery were excluded [47, 64]. Finally, studies were excluded if the primary outcome was not included in the list described above [7, 48].

We used a templated evidence-based medicine literature review form to assist in the systematic review of articles and in the data collected. Demographic data extracted for comparison included year of publication, author, total number of subjects, mean patient age, percent male, and comorbidity. The intervention (specific RA and/or regional analgesia technique) and comparator (GA and/or specific systemic analgesia technique) were recorded. Each outcome then was evaluated qualitatively for each intervention and comparator and the data recorded in tables. Because there were a limited number of studies with homogenous design for each outcome, meta-analysis was not performed.

Several criteria were used to assess the quality of each trial. The likelihood of methodologic bias of each RCT was assessed using the Jadad score, which assigns points based on three factors [39]. One point was given to randomized studies, an additional point was given if the method of randomization was described and appropriate, and one point was deducted if randomization was inappropriate. One point was given if a study was double-blind, and an additional point was given if the blinding procedure was described and appropriate. One point was deducted if blinding was inappropriate. One point was given if the numbers and reasons for withdrawals were described. The maximum score is 5; trials scoring 3 or more generally are regarded as having satisfactory methodologic quality. Allocation concealment, which helps eliminate selection bias, was assessed and defined as adequate, unclear, or inadequate. Finally, whether patient followup rates were less than 80% was recorded.

After abstraction of information, a level of evidence (see Guidelines for Authors) was assigned to the outcomes of each RCT (Level I is a high-quality RCT; Level II is a

lesser-quality RCT, eg, less than 80% followup, no blinding, or improper randomization). Two authors (AJRM, RB) independently reviewed and scored each RCT using the aforementioned methodology.

Results

We identified 28 RCTs that compared either GA versus RA and/or systemic versus regional analgesia for TKA (Fig. 1). The 28 studies included 1538 patients. Fourteen of these had a Jadad score of 2 or less. Allocation concealment was unclear in 27 trials and inadequate in one. In one RCT, the dropout of participants was greater than 20% (Table 1). Eleven of the 28 RCTs were considered to provide Level I evidence. We summarized the 11 outcomes in each of the 28 trials and noted the Level of Evidence and the direction of difference between the two types of anesthesia (Table 2).

Only one trial (comparing epidural anesthesia and GA) recorded mortality (during the first 8 weeks postoperatively) as a secondary outcome [83]; the authors observed no difference with one death in each group (Level II) [83]. There are no recent RCTs primarily designed to assess differences in mortality after GA versus RA for TKA.

Nine trials examined cardiovascular morbidity, always as a secondary outcome. In the three that recorded postoperative myocardial infarction and pulmonary edema, there was no difference between the two anesthetic techniques (Level II) [16, 73, 83]. The incidence of postoperative hypotension was recorded in eight studies (Table 3). In three of the six that compared epidural analgesia with either systemic analgesia or other methods

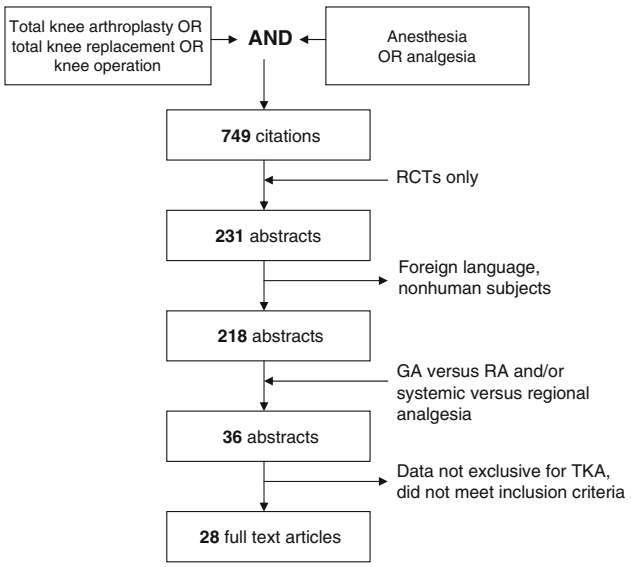

Fig. 1 A flowchart shows the included and excluded studies.

of regional analgesia, there was more postoperative hypotension in the epidural group (Level I).

When chemical thromboprophylaxis was administered, there was no difference in the incidence of DVT (Table 4) or PE (Table 5) between GA and RA for TKAs (Level II) [16, 21, 57, 82]. In one Level I study, there was a decreased incidence of DVT in favor of RA; however, no chemical thromboprophylaxis was used [41].

Of the five RCTs that addressed perioperative blood loss, none reported a difference in either blood loss or transfusion requirements with RA compared with GA (Level II) [6, 16, 41, 57, 63].

The duration of surgery was not influenced by the type of anesthetic for TKA (Level II) [6, 14, 16, 25, 45, 57, 59, 61, 63, 70, 72, 82, 83].

Our review identified 24 RCTs that compared systemic and regional analgesia for TKA, and in 21 of these trials, RA reduced pain scores and/or morphine consumption. Epidural analgesia (Level I), single-injection FNB (Level I) either with or without sciatic nerve block (Level II), continuous catheter-based FNB (CFNB) (Level II), and continuous psoas plexus block (Level II) were superior to systemic analgesia (Table 6) [2, 6, 14, 16, 18, 21, 25, 28, 35, 44, 56, 59, 61, 69, 70, 74, 76, 79]. One Level I study only reported an analgesic benefit (reduced pain scores) from FNB compared with systemic analgesia when the FNB was combined with an obturator nerve block [50]. Obturator block alone was of no value (Level II) [45]. When reported, the analgesic benefit after single-shot PNBs compared with systemic analgesia lasted as much as 48 hours. The effect of CFNB on pain scores varied in different studies from a reduction in the recovery area only to as much as 48 hours. Epidural analgesia was effective in reducing pain scores for as much as 10 days when the infusion was continued for 7 days postoperatively [21]. Only one study included a comparison of single-injection FNB with CFNB for postoperative analgesia after TKA [35]. In this study, placement of a catheter provided little additional benefit, although this finding has since been countered in the literature [68, 80].

Eighteen trials reported opioid-related adverse effects, and although all were analyzed as secondary outcomes, there was evidence that FNB (Level I), FNB plus obturator block (Level I), FNB plus sciatic block (Level I), CFNB (Level II), and epidural analgesia (Level II) reduced opioid-related adverse effects (Table 7) [21, 35, 50, 56, 76, 79]. Specifically, postoperative nausea and vomiting and sedation were less frequent in the RA groups. Urinary retention, however, was, in two studies, greater in patients who received epidural analgesia compared with patients who received PNB and systemic analgesia (Level II) [14, 74]. Pruritis also was increased, compared with systemic analgesia, in one of the three studies in which

Table 1. Demographic data, design, and breakdown of Jadad score for each trial

Study (year)	Number	Anesthesia	Analgesia	Age (years)*	% Male	Comorbidity	Allocation concealed	Jadad score	Remarks
Good et al. [28] (2007)	21	Undisclosed	FNB†	61 (13)	64	NA	Unclear	10111 (4)	
	21	Undisclosed	Placebo†	68 (10)	60				
Kardash et al. [45] (2007)	19	SA	FNB†	65 (2)	21	Morbid obesity or renal failure excluded	Unclear	11111 (5)	
	20	SA	OB†	72 (2)	20				
	20	SA	Sham + IV PCA†	67 (1)	25				
Seet et al. [69] (2006)	17	SA	CFNB 0.15% R†	67 (8)	12	ASA 1–3 Weight < 120 kg	Unclear	10001 (2)	CFNB continued for 48 hours
	18	SA	CFNB 0.2% R†	65 (8)	28				
	20	SA	IV PCA†	68 (5)	20				
Chu et al. [16] (2006)	30	CSE†	CEA†	62 (62–68)		ASA 1–3	Unclear	10001 (2)	CEA continued "at least" 48 hours; patients immobilized first 48 hours
	30	GA†	IV PCA†	69 (62–74)					
Tugay et al. [77] (2006)	8	GA	Preoperative FNB†	68 (6)	13	ASA 1–3	Unclear	10000 (1)	
	7	GA	Postoperative FNB†	67 (7)	25				
	8	GA	IV PCA†	63 (7)	0				
Axelsson et al. [6] (2005)	15	EA	CEA 0.125% R†	72 (7)	40	ASA 1–2	Unclear	11111 (5)	CEA continued for 48 hours
	15	EA	CEA 0.2% R†	70 (8)	40				
	15	EA	Placebo†	70 (8)	27				
Szczukowski et al. [76] (2004)	19	GA	FNB†	68	37	ASA 1–3	Unclear	11110 (4)	
	21	GA	Sham injection + IV PCA†	66	38				
Kaloul et al. [44] (2004)	20	SA	CFNB†	67 (12)	40	ASA 1–3	Unclear	11000 (2)	CFNB and CPB continued for 48 hours
	20	SA	CPB†	69 (7)	35				
	20	SA	IV PCA†	70 (5)	35				
Farag et al. [21] (2005)	21	EA†	CEA†	63 (8)	19	ASA 1–3	Unclear	11001 (3)	CEA continued for 7 days; no intention to treat analysis in epidural group
	22	SA†	IV PCA†	64 (13)	41				
Macalou et al. [50] (2004)	29	GA	FNB†	68 (9)	24	ASA 1–3 Morbid obesity excluded	Unclear	11001 (3)	Study limited to 6 hours postoperatively
	33	GA	FNB + OB†	71 (9)	12				
	28	GA	Sham injection + IV PCA†	70 (7)	29				
Adams et al. [1] (2002)	21	GA	3-in-1 FNB†	70	24	ASA 1–3	Unclear	10001 (2)	Single-dose EA
	21	GA	EA†	69	33				
	21	GA	IV PCA†	69	33				
Wang et al. [79] (2002)	15	GA	FNB†	66 (10)	33	ASA 2–3 Age 40–70 years	Unclear	11110 (4)	
	15	GA	Placebo†	67 (8)	40				

Table 1. continued

Study (year)	Number	Anesthesia	Analgesia	Age (years)*	% Male	Comorbidity	Allocation concealed	Jadad score	Remarks
McNamee et al. [56] (2001)	25	SA	FNB + SNB B†	69 (58–83)	36	ASA 1–3	Unclear	11111 (5)	0.75 mg spinal diamorphine in all groups
	25	SA	FNB + SNB R†	68 (47–83)	40				
	24	SA	IV PCA†	70 (54–84)	29				
Ng et al. [61] (2001)	12	GA	3-in-1 FNB R 0.25%†	64 (8)	8	ASA 1–2 Weight < 100 kg	Unclear	11110 (4)	
	12	GA	3-in-1 FNB R 0.5%†	65 (5)	17				
	12	GA	3-in-1 FNB B 0.25%†	63 (8)	8				
	12	GA	Sham + IV PCA†	65 (14)	25				
Capdevila et al. [14] (1999)	20	GA	CFNB†	58 (16)	53	ASA 1–2 Age 18–70 years	Unclear	10000 (1)	CFNB and CEA continued for 72 hours
	17	GA	CEA†	54 (17)	40				
	19	GA	IV PCA†	51 (15)	59				
Ganapathy et al. [25] (1999)	20	SA	CFNB 0.2% B†	70 (9)	45	ASA 1–3 Age 18–80 years	Unclear	10110 (3)	CFNB continued for 48 hours
	20	SA	CFNB 0.1% B†	66 (6)	45				
	22	SA	Placebo†	66 (11)	59				
Singelyn et al. [74] (1998)	15	GA	CFNB†	NA	NA	ASA 2–3 Age 18–80 years Diabetics excluded	Unclear	11000 (2)	CFNB and CEA continued for 48 hours; age and gender "comparable in all groups"
	15	GA	CEA†						
	15	GA	IV PCA†						
Allen et al. [2] (1998)	12	SA	FNB + IV PCA†	66 (8)	67	ASA 1–2 Age 40–80 years Weight < 140 kg	Unclear	10110 (3)	
	12	SA	FNB + SNB + IV PCA†	69 (6)	50				
	12	SA	Sham injections + IV PCA†	68 (6)	67				
Williams-Russo et al. [82] (1996)	97	EA†	CEA†	68 (8)	26	Charlson comorbidity score 0 in 60% of both groups Age > 40 years	Unclear	11001 (3)	Subset of study population in Reference 83
	81	GA†	IV opioid†	68 (9)	35				
Hirst et al. [35] (1996)	11	GA	FNB + IV PCA†	67 (12)	36	ASA 1–3	Unclear	10110 (3)	CFNB continued for 48 hours
	11	GA	CFNB + IV PCA†	71 (12)	27				
	11	GA	IV PCA†	70 (7)	27				
Williams-Russo et al. [83] (1995)	134	EA†	CEA†	69	29	Charlson comorbidity score 0 in 59% of EA and 62% of GA groups Age > 40 years	Unclear	11001 (3)	CEA continued for between 12 and 72 hours
	128	GA†	IV opioid†	69	30				
Sharrock et al. [73] (1994)	26	EA	CEA†	69 (7)	50	ASA 1–3	Unclear	11001 (3)	CEA discontinued on POD 2; bilateral TKA
	25	EA	IV opioid†	68 (7)	40				

Table 1. continued

Study (year)	Number	Anesthesia	Analgesia	Age (years)*	% Male	Comorbidity	Allocation concealed	Jadad score	Remarks
Moiniche et al. [59] (1994)	10	EA†	CEA†	77 (70–81)	30	No apparent exclusions	Unclear	11000 (2)	CEA continued for 48 hours
	10	GA†	IM morphine†	77 (66–81)	40				
Edwards and Wright [18] (1992)	19	GA	CFNB†	69 (9)	37	Only exclusion criteria were severe cardiorespiratory disease, hepatic or renal impairment	Unclear	10001 (2)	CFNB continued for 24 hours
	18	GA	IM opioid†	66 (6)	44				
Jorgensen et al. [41] (1991)	17	EA†	CEA†	70.5 (52–87)	24	Exclusions were premenopausal women, those on antithrombotic medication	Unclear	10001 (2)	CEA continued until POD 3
	22	GA†	IM opioid†	64 (38–85)	32				
Serpell et al. [70] (1991)	13	SA	CFNB + IV PCA†	68	15	ASA 1–2	Unclear	10001 (2)	Intermittent boluses for 48 hours
	16	SA	IV PCA†	70	25				
Mitchell et al. [57] (1991)	34	EA†	Undisclosed	64	63	Age > 40 years	Inadequate	1–1000 (0)	Inappropriate method of randomization
	38	GA†	Undisclosed						
Nielson et al. [63] (1990)	25	SA†	Opioid	68 (6)		ASA 1–3 Age 60–86 years	Unclear	10001 (2)	More than 20% dropout
	39	GA†	Opioid	70 (6)					

* Age presented as mean (standard deviation) or median (range) where available; †randomization groups; FNB = femoral nerve block; NA = not available; SA = systemic analgesia; OB = obturator nerve block; IV = intravenous; PCA = patient-controlled analgesia; CFNB = continuous femoral nerve block; ASA = American Society of Anesthesiologists; CSE = combined spinal epidural; CEA = continuous epidural analgesia; GA = general anesthesia; EA = epidural anesthesia; R = ropivicaine; CPB = continuous psoas block; SNB = sciatic nerve block; B = bupivicaine; POD = postoperative day; IM = intramuscular.

Table 2. Outcomes and levels of evidence for each study included in the review*

Study (year)	Anesthesia	Analgesia	Mortality	Outcomes (levels of evidence)									
				CVS	DVT	PE	Blood loss	Duration surgery	Pain	Adverse effects	Cognitive deficit	LOS	Rehabilitation
Good et al. [28] (2007)	Not disclosed	FNB†							↔ (II) ↓ MC (I)	↔ (II)			↔ (II)
	Not disclosed	Placebo†											
Kardash et al. [45] (2007)	SA	FNB†						↔ (II)	↓ (I) FNB only	↔ (II)		↔ (II)	↔ (II)
	SA	Obturator block†											
	SA	Sham + IV PCA†											
Seet et al. [69] (2006)	SA	CFNB 0.15% R†		↔ (II)					↔ (II)↓ MC (I)	↔ (II)		↔ (II)	↔ (II)
	SA	CFNB 0.2% R†											
	SA	IV PCA†											
Chu et al. [16] (2006)	CSE†	EA†		↔ (II)	↔ (II)		↔ (II)	↔ (II)	↓ (I)	↔ (II)		↔ (II)	↔ (II)
	GA†	IV PCA†											
Tugay et al. [77] (2006)	GA	Preoperative FNB†							↓ (II)			↔ (II)	↔ (II)
	GA	Postoperative FNB†											
	GA	IV PCA†											
Axelsson et al. [6] (2005)	EA	CEA†		↑ (I)			↔ (II)	↔ (II)	↓ (I) ↓ MC (I)	↑ (I)			↔ (II)
	EA	CEA†											
	EA	Placebo†											
Szczukowski et al. [76] (2004)	GA	FNB†							↓ MC (I)	↔ (II)		↔ (II)	↔ (II)
	GA	Sham + IV PCA†											
Kaloul et al. [44] (2004)	SA	CFNB†							↓ (II) ↓ MC (II)				
	SA	CPB†											
	SA	IV PCA†											
Farag et al. [21] (2005)	EA†	CEA†			↔ (II)				↓ (II)	↓ (II)			
	SA†	IV PCA†											
Macalou et al. [50] (2004)	GA	FNB†		↔ (II)					↓ (I) FNB + OB only	↓ (I)			
	GA	FNB + OB†											
	GA	Sham + IV PCA†											
Adams et al. [1] (2002)	GA	3-in-1 FNB†		↑ (II)					↔ (II)	↔ (II)			
	GA	EA†											
	GA	IV PCA†											
Wang et al. [79] (2002)	GA	FNB†						↔ (II)	↓ (I) ↓ MC (I)	↓ (I)		↓ (I)	↓ (I)
	GA	Placebo†											

Table 2. continued

Study (year)	Anesthesia	Analgesia	Mortality	Outcomes (levels of evidence)									
				CVS	DVT	PE	Blood loss	Duration surgery	Pain	Adverse effects	Cognitive deficit	LOS	Rehabilitation
McNamee et al. [56] (2001)	SA	FNB + SNB B†							↓ (I) ↓ MC (I)	↓ (II)			
	SA	FNB + SNB R†											
	SA	IV PCA†											
Ng et al. [61] (2001)	GA	3-in-1 FNB R 0.25%†						↔ (II)	↓ (I) ↓ MC (I)	↔ (II)			↔ (II)
	GA	"3-in-1" FNB R 0.5%†											
	GA	3-in-1 FNB B 0.25%†											
	GA	Sham + IV PCA†											
Capdevila et al. [14] (1999)	GA	CFNB†		↑ (II)				↔ (II)	↓ (II)	↓ (II)/ ↑ (II)		↓ (II)	↓ (I)
	GA	CEA†											
	GA	IV PCA†											
Ganapathy et al. [25] (1999)	SA	CFNB 0.2% B†						↔ (II)	↓ (I) ↓ MC (I) 0.2% B only	↔ (II)			↓ (I)
	SA	CFNB 0.1% B†											
	SA	Placebo†											
Singelyn et al. [74] (1998)	GA	CFNB†		↔ (II)					↓ (II)	↑ (II)		↓ (II)	↓ (II)
	GA	CEA†											
	GA	IV PCA†											
Allen et al. [2] (1998)	SA	FNB + IV PCA†							↓ (I) ↓ MC (I)	↔ (II)			
	SA	FNB + SNB + IV PCA†											
	SA	Sham injections + IV PCA†											
Williams-Russo et al. [82] (1996)	EA†	CEA†			↔ (II)	↔ (II)		↔ (II)				↔ (II)	↓ (II)
	GA†	IV opioid†											
Hirst et al. [35] (1996)	GA	FNB + IV PCA†							↓ (I) ↔ MC (II)	↓ (II)			
	GA	CFNB + IV PCA											
	GA	IV PCA†											
Williams-Russo et al. [83] (1995)	EA†	CEA†	↔ (II)	↔ (II)				↔ (II)			↔ (II)		
	GA†	IV opioid†											
Moiniche et al. [59] (1994)	EA†	CEA†						↔ (II)	↓ (II)			↔ (II)	↔ (II)
	GA†	IM morphine†											
Sharrock et al. [73] (1994)	EA	CEA†		↔ (II)					↓ (II)			↔ (II)	↔ (II)
	EA	IV opioid†											
Edwards and Wright [18] (1992)	GA	CFNB†							↔ (II) ↓ MC (II)				
	GA	IM opioid†											

Table 2. continued

Study (year)	Anesthesia	Analgesia	Mortality	Outcomes (levels of evidence)									
				CVS	DVT	PE	Blood loss	Duration surgery	Pain	Adverse effects	Cognitive deficit	LOS	Rehabilitation
Jorgensen et al. [41] (1991)	EA†	CEA†			↓ (I)	↔ (II)	↔ (II)						
	GA†	IM opioid†											
Serpell et al. [70] (1991)	SA	CFNB + IV PCA†						↔ (II)	↔ (II) ↓ MC (II)	↔ (II)			
	SA	IV PCA†											
Mitchell et al. [57] (1991)	EA†	Undisclosed			↔ (II)	↔ (II)	↔ (II)	↔ (II)				↔ (II)	
	GA†	Undisclosed											
Nielson et al. [63] (1990)	SA†	Opioid					↔ (II)	↔ (II)	↔ MC (II)		↔ (II)		
	GA†	Opioid											

* Arrows indicate whether the outcome is no different (↔), better (↓), or worse (↑) with regional anesthesia and/or regional analgesia compared with general anesthesia and/or systemic analgesia; †randomization groups; CVS = cardiovascular morbidity; DVT = deep venous thrombosis; PE = pulmonary embolus; LOS = length of stay; FNB = femoral nerve block; MC = morphine consumption; SA = spinal anesthesia; IV = intravenous; PCA = patient-controlled analgesia; CFNB = continuous femoral nerve block; R = ropivicaine; CSE = combined spinal epidural; EA = epidural anesthesia; GA = general anesthesia; CEA = continuous epidural analgesia; CPB = continuous psoas block; OB = obturator nerve block; SNB = sciatic nerve block; B = bupivicaine; IM = intramuscular.

epidural opioids were combined with local anesthetic in the infusion (Level II) [6]. In 10 of the 18 studies, there were no differences in adverse effects between the GA and RA groups (Level II), although frequently there were trends toward a benefit of RA [1, 2, 16, 25, 28, 35, 45, 61, 69, 70].

In the two studies that examined short-term (1 week) or long-term (3 and 6 months) cognitive function, the anesthetic technique made no difference (Level II) [63, 83].

Of the 12 RCTs that examined length of stay, one Level I and two Level II studies found CFNB or FNB can reduce length of hospital stay by up to 1 day and/or length of rehabilitation center stay by up to 13 days (Table 8) [14, 74, 79]. The remainder of the studies reported no difference, but these were all Level II evidence.

Among the 14 studies that investigated postoperative rehabilitation for TKA, six reported RA improved this process compared with GA (Table 9) [14, 25, 69, 74, 79, 82]. There was Level I evidence that range of motion and ambulation were improved by either FNB or CFNB. Epidural analgesia and CFNB can help to attain rehabilitation milestones earlier than intravenous patient-controlled analgesia [17].

Discussion

The aim of this systematic review was to examine the best available evidence comparing GA and/or systemic analgesia versus RA and/or regional analgesia for TKAs. The specific questions we sought to answer were whether, when compared with GA and/or systemic analgesia, RA and/or regional analgesia for TKAs decreased mortality, cardiovascular morbidity, DVT and PE, blood loss, duration of surgery, pain, opioid-related adverse effects, cognitive defects, and length of stay. We also wanted to know if RA improved rehabilitation.

Before further considering the implications of our review, we accept there are several limitations. First, for practical reasons, we chose to include only English language trials. Although this may have introduced bias, Juni et al. [42] suggested excluding trials not published in English has little effect on summary treatment effect estimates. Second, we found 14 of the 28 RCTs evaluated here had Jadad scores of 2 or less. However, not all of these trials were of poor methodologic quality. For example, when studying PNBs for systemic analgesia, sham nerve blocks often are not administered for ethical reasons. Regardless, the Jadad score is effectively reduced automatically by 2 points for the lack of a double-blinded study design. Third, we identified no large ($n > 1000$) trials. The studies included in our review had sample sizes varying from only 20 to 262 patients. In trials with small numbers of subjects, the absence of significant differences in

Table 3. General anesthesia versus regional anesthesia and/or systemic versus regional analgesia for TKA: cardiovascular morbidity*

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Seet et al. [69] (2006)	Hypotension	CFNB 0.15%B (18), CFNB 0.2% B (6), IV PCA (15)	0.60	2°	II	Hypotension defined as < 15% baseline
Chu et al. [16] (2006)	MI	CEA (0), IV PCA (0)	NS	2°	II	Hypotension defined as < 20% of baseline
	Hypotension	CEA (53), IV PCA (63)	0.43	2°	II	
Axelsson et al. [6] (2005)	Hypotension	"Minor but significant decrease in systolic pressure (16%–22%)" in high dose CEA during 9–18 hours postoperatively compared with lower dose CEA and placebo	< 0.05	2°	I	Hypotension defined as < 30% of baseline or systolic pressure < 80 mm Hg; observations continued for 48 hours postoperatively
Macalou et al. [50] (2004)	Hypotension 6 hours	FNB (0), FNB + OB (3), IV PCA (0)	NS	2°	II	Hypotension defined as requiring sympathomimetic drugs
Adams et al. [1] (2002)	Systolic arterial pressure	Significantly less in CEA vs FNB and IV PCA at 15, 30, 60, and 120 minutes	< 0.001	2°	II	Measurements only up to 180 minutes postoperatively
Capdevila et al. [14] (1999)	Hypotension 24 hours	CFNB (50), CEA (76),†,‡ IV PCA (26)	< 0.05	2°	II	Hypotension defined as < 20% baseline; observations continued for 72 hours; no significant differences beyond times stated
	Hypotension 48 hours	CFNB (17), CEA (23.5),†,‡ IV PCA (13)	< 0.05			
Singelyn et al. [74] (1998)	Hypotension	CFNB (0), CEA (7), IV PCA (0)	0.36	2°	II	Hypotension not defined
Williams-Russo et al. [83] (1995)	MI	EA (2.2), GA (2.3)	NS	2°	II	No difference also in cardiopulmonary arrest
	Pulmonary edema	EA (0.7), GA (0)	NS	2°	II	
Sharrock et al. [73] (1994)	MI	CEA (4), IV analgesia (0)	NS	2°	II	Hypotension defined as < 90 mm Hg and requiring vasopressors
	Hypotension	CEA (27), IV analgesia (24)	NS	2°	II	
Nielson et al. [63] (1990)	Blood pressure (mm Hg)	SA (127), GA (130)	NS	2°	II	Intraoperative pressure only; unclear how this number was derived

* Results are expressed as percentage of incidence unless stated otherwise; †vs IV PCA; ‡vs CFNB; p values provided where available; OUT = outcome; LoE = level of evidence; CFNB = continuous femoral nerve block; IV = intravenous; PCA = patient-controlled analgesia; MI = myocardial infarction; CEA = continuous epidural analgesia; NS = not significant; FNB = femoral nerve block; EA = epidural anesthesia; GA = general anesthesia; SA = spinal anesthesia; 1° = primary; 2° = secondary.

Table 4. General anesthesia versus regional anesthesia and/or systemic versus regional analgesia for TKA: perioperative deep venous thrombosis*

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Chu et al. [16] (2006)	DVT incidence	CSE (0), GA (0)	NS	2°	II	Clinical diagnosis. All patients not routinely scanned with Doppler ultrasound or venography; both groups received low molecular weight heparin
Farag et al. [21] (2005)	DVT incidence POD 3	CEA (0), IV PCA (0)	NS	2°	II	All patients underwent routine Doppler ultrasonography at PODs 3 and 10; all patients had compression stockings and IV PCA group also received low molecular weight heparin; significantly underpowered for this outcome
	DVT incidence POD 10	CEA (0), IV PCA (0)				
Williams-Russo et al. [82] (1996)	Postoperative positive venography	EA (40), GA (48) *All DVTs were below knee*	0.3	2°	II	Subset of study population in Reference 83; blinding of radiologists only; sample size powered for cognitive function tests; daily ASA thromboprophylaxis, graded elastic stockings, and early mobilization
Jorgensen et al. [41] (1991)	Overall incidence of DVT	EA (15), GA (59)	0.02	1°	I	Followup 81%; compression stockings
	Calf vein thrombosis	EA (12), GA (45)	0.05			
	Symptomatic DVT (number of patients)	EA (0), GA (2)	NS			
Mitchell et al. [57] (1991)	Combined radiologic DVT or PE	EA (35), GA (25)	> 0.05	1°	II	Inappropriate method of randomization; daily ASA thromboprophylaxis (males) or low-dose warfarin (females); no clinical episodes of thromboembolic disease
	Proximal vein thrombosis	EA (46), GA (64)				

* Results are expressed as percentage of patients unless stated otherwise; p values provided where available; LoE = level of evidence; DVT = deep vein thrombosis; CSE = combined spinal epidural; GA = general anesthesia; NS = not significant; POD = postoperative day; CEA = continuous epidural analgesia; IV = intravenous; PCA = patient-controlled analgesia; EA = epidural anesthesia; ASA = aspirin; PE = pulmonary embolus; 1° = primary; 2° = secondary.

secondary outcomes must be interpreted with caution, because these studies are often inadequately powered to detect such differences [52]. Lack of evidence is not the same as evidence of absence and therefore secondary outcomes are highlighted in the summary tables. These shortcomings also are reflected in the level of evidence scores (ie, by definition, Level II). Finally, the purpose of this review was not to provide recommendations on the preferred mode of anesthesia for TKA. To do so would have required an assessment of harm and consideration of other information such as costs, quality of life, and feasibility. One major concern with RA is the risk of nerve injury compared with GA. This is difficult to quantify and has been addressed elsewhere [13]. As with any anesthetic technique, patient preference and expertise of the anesthesiologist also must be considered.

The lack of difference in mortality between GA and RA for TKA is unsurprising to us given the safety of modern anesthetic and surgical practices. Much greater numbers than those included in the one RCT that we identified would be required to show any difference. In a large meta-analysis comparing GA and CNB for various types of surgery, Rodgers et al. [67] reported overall mortality was reduced by ⅓ (odds ratio, 0.70; 95% confidence interval, 0.54–0.90) in patients allocated to CNB. When each surgical group in this meta-analysis was analyzed individually, there was decreased mortality only in the orthopaedic group [67]. Overall mortality was reduced

Table 5. General anesthesia versus regional anesthesia and/or systemic versus regional analgesia for TKA: perioperative pulmonary embolus*

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Williams-Russo et al. [82] (1996)	Radiologic PE	EA (12), GA (9)	0.6	2°	II	Subset of study population in Reference 83; minus those who had DVT on venography; blinding of radiologists only; daily ASA thromboprophylaxis, graded elastic stockings, and early mobilization
Jorgensen et al. [41] (1991)	Nonfatal PE (number of patients)	EA (0), GA (1)	NS	2°	II	Inadequate sample size; compression stockings
Mitchell et al. [57] (1991)	Combined radiologic DVT or PE	EA (35), GA (25)	> 0.05	1°	II	Inappropriate method of randomization; daily ASA thromboprophylaxis (males) or low-dose warfarin (females); no clinical episodes of thromboembolic disease

* Results are expressed as percentage of patients unless stated otherwise; p values provided where available; LoE = Level of Evidence; PE = pulmonary embolus; EA = epidural anesthesia; GA = general anesthesia; DVT = deep vein thrombosis; ASA = aspirin; NS = not significant; 1° = primary; 2° = secondary.

regardless whether CNB was continued postoperatively. Conversely, combined intraoperative GA and CNB negated the mortality benefit of CNB alone.

Three RCTs examined cardiovascular morbidity other than hypotension in TKA and compared GA and RA. The lack of difference in these trials could have been the result of inadequate numbers of patients. In the meta-analysis by Rodgers et al. [67], there was a reduction in the incidence of myocardial infarction in the epidural group, although the confidence interval just reached zero. This difference was detected only when all surgical groups were combined and did not specifically apply to orthopaedic patients alone. Additional RCTs with large numbers are needed to examine whether RA reduces serious cardiovascular morbidity in TKA. Although three trials detected an increased frequency of hypotension in patients undergoing epidural analgesia compared with other methods of regional or systemic analgesia, there was no information regarding whether this resulted in any other morbidity. Two of these trials were included in a recent meta-analysis, which concluded epidural analgesia for TKA caused more hypotension than PNBs (odds ratio, 0.19; 95% confidence interval, 0.08–0.45) [23].

Although a recent meta-analysis showed the incidence of DVT in THA was reduced by using RA compared with GA, there are no similar meta-analyses for TKA [54]. In the only study we found that had a decreased incidence of DVT with RA, patients did not receive chemical thromboprophylaxis [41]. Four studies reported no difference in the incidence of DVT, but two were inadequately powered and the others were of poor quality [16, 21, 57, 82]. In a subset of patients in one of these trials, there was no difference in plasma markers of thrombin generation or fibrinolytic activity between the GA and RA groups [72]. Another study, however, measured laboratory parameters of coagulation and reported an increase in coagulability in the GA group compared with RA [48]. Unfortunately these authors did not seek to formally diagnose DVT or PE in their study. It has been suggested CNB may decrease the incidence of DVT either directly by enhancing lower extremity venous blood flow or indirectly by facilitating postoperative rehabilitation after TKA, but additional work is required to ascertain whether RA offers any additive benefit when used in combination with contemporary preventive strategies such as routine thromboprophylaxis and rapid postoperative mobilization. Although no difference occurred between GA and RA in the three trials that compared the incidence of PE, the method of randomization was inadequate in one trial and the sample size was inadequate in the other two.

Although we found no difference in blood loss or transfusion requirements with RA compared with GA, all studies were of poor methodologic quality or had inadequate sample sizes. Furthermore, intraoperative blood loss in TKA is minimal because of the use of a tourniquet and only two studies actually extended measurements into the postoperative period [16, 41]. Blood loss in TKA is multifactorial and it is not clear therefore if RA can offer any additional benefit [43].

Our systematic review revealed RA reduced postoperative pain, particularly on movement, in TKA. Even when no differences in pain scores were reported between the systemic and regional analgesia, patient satisfaction scores still favored CFNB compared with intravenous patient-controlled analgesia [69]. Choi et al. [15] published a meta-analysis comparing postoperative epidural analgesia with systemic analgesia after THA or TKA. They concluded epidural analgesia provided better pain relief only for up to

Table 6. General anesthesia versus regional anesthesia and/or systemic versus regional analgesia for TKA: postoperative pain*

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Good et al. [28] (2007)	Mean VAS POD 1	FNB (4.7), placebo (5.3)	0.20	2°	II	Powered for morphine consumption; trends suggested improved pain scores in FNB group but not significant
	Mean VAS POD 2	FNB (4.0), placebo (4.9)	0.08			
	Mean VAS POD 3	FNB (3.9), placebo (3.4)	0.767			
	24-hour morphine consumption (mg)	FNB (22.5), placebo (37.5)	0.016	1°	I	
Kardash et al. [45] (2007)	NRS rest recovery room, 24 hours, 48 hours	No difference between FNB, obturator and IV PCA	NS	1°	I	Only 75% of FNB group had sensory block to anterior thigh; reduced pain in FNB compared with IV PCA in recovery room when analyzed as difference from baseline pain scores ($p = 0.02$); no differences between groups in pain scores from 24 hours onwards
	NRS movement recovery room, 24 hours, 48 hours	Less in FNB compared to obturator in recovery room. No difference at other times	0.03	2°	I	
	Opioid consumption	No difference between groups	NS	2°	I	
Seet et al. [69] (2006)	VAS rest (0–72 hours)	No difference among all 3 groups	0.274	2°	II	Powered for morphine consumption
	VAS movement (0–72 hours)	No difference among all 3 groups	0.826	1°	II	
	Overall morphine consumption	Reduced in CFNB 0.15% R vs IV PCA	< 0.0005			
	Overall morphine consumption	Reduced in CFNB 0.2% R vs IV PCA	0.0023			
Chu et al. [16] (2006)	NRS at 1, 8, 24, 48 hours	Reduced in CEA vs IV PCA at 1, 12 and 48 hours	< 0.05	1°	II	
Tugay et al. [77] (2006)	VAS (0–48 hours)	Reduced in preoperative FNB vs IV PCA	0.018	2°	II	No difference between preoperative and postoperative FNB
	VAS (0–48 hours)	Reduced in postoperative FNB vs IV PCA	0.001	2°	II	
	Total morphine consumption	No difference between FNB and IV PCA	> 0.05	2°	II	
Axelsson et al. [6] (2005)	VAS rest	Reduced in CEA 0.2% R vs placebo at 3–15 hours and 0.125% R vs placebo at 3–6 hours	< 0.05	1°	I	All patients received preoperative oxycodone; 0.02 mg/mL epidural morphine in both R infusions also; measurements continued for 48 hours postoperatively; significantly less pain scores at rest and during movement in 0.2% R vs 0.125% R
	VAS movement	Reduced in CEA 0.2% R vs placebo at 3–27 hours and 0.125% R vs placebo at 9–18 hours	< 0.05	1°	I	
	Morphine consumption	Reduced in CEA 0.2% R and 0.125% R vs placebo up to 48 hours	< 0.001	2°	I	
Szczukowski et al. [76] (2004)	Mean VAS day of surgery	FNB (4.07), sham (6.00)	0.002	2°	I	No difference in pain scores on POD 1 or 2
	Average VAS over 3 days	FNB (3.67), sham (4.78)	0.013	2°	I	
	Morphine consumption DOS (mg)	FNB (48.1), sham (76.2)	0.003	1°	I	
	Morphine consumption POD 1 (mg)	FNB (26.3), sham (40.3)	0.022	2°	I	
	Morphine consumption POD 2 (mg)	FNB (14.1), sham (20.3)	0.160	2°	II	
	Total postoperative morphine consumption (mg)	FNB (84.9), sham (141.7)	0.011	2°	II	

Table 6. continued

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Kaloul et al. [44] (2004)	VAS rest	Reduced in both CFNB and CPB compared to IV PCA at 6 and 24 hours; no difference at 48 hours	0.0001	2°	II	No difference in pain scores or morphine consumption between CFNB and CPB; no difference in satisfaction between all three groups
	VAS physiotherapy	CFNB (4.1), CPB (4.2), IV PCA (4.1)	NS	2°	II	
	Total morphine consumption at 48 hours	Reduced in CFNB vs IV PCA by 48%	0.0002	1°	II	
	Total morphine consumption at 48 hours	Reduced in CPB vs IV PCA by 50%	0.0001	1°	II	
Farag et al. [21] (2005)	VAS rest	Lower in CEA (2.8) vs IV PCA (4.9) on POD 1 only	0.001	2°	II	Pain measured for 10 days postoperatively
	VAS movement	Lower in CEA vs IV PCA after adjustment for day of surgery	0.001	2°	II	
Macalou et al. [50] (2004)	Mean VAS rest 0 hour	Less in FNB + OB vs FNB and IV PCA	0.0018	1°	I	Pain scores below 3 in all groups after 2 hours; significantly less morphine requests in FNB + OB group also vs FNB and IV PCA
	Mean VAS rest 1 hour	Less in FNB + OB vs FNB and IV PCA	0.0055			
	Mean VAS rest 2 hour	Less in FNB + OB vs FNB and IV PCA	0.0003			
	Mean VAS rest 4 hour	Less in FNB + OB vs FNB and IV PCA	0.0166			
	Mean VAS rest 6 hour	Less in FNB + OB vs FNB and IV PCA	0.0257			
Wang et al. [79] (2002)	Mean VAS rest POD 1	FNB (2.7), placebo (5.5)	< 0.01	1°	I	Trend toward reduction in pain scores POD 2 and 3
	Mean VAS rest POD 2	FNB (1.4), placebo (2.6)	NS			
	Mean VAS rest POD 3	FNB (0.3), placebo (1.0)	NS			
	Mean VAS movement POD 1	FNB (6.2), placebo (7.8)	< 0.05			
	Mean VAS movement POD 2	FNB (3.7), placebo (4.5)	NS			
	Mean VAS movement POD 3	FNB (1.8), placebo (3.1)	NS			
	Total postoperative morphine consumption (mg/kg)	FNB (0.7), placebo (2.5)	< 0.05			
Adams et al. [1] (2002)	Mean VAS	No difference among FNB, CEA, or IV PCA at any time from 0–180 minutes postoperatively	NS	2°	II	Pain scores only measured up to 180 minutes; significantly higher plasma epinephrine levels in PCA group vs 3-in-1 or EA; no difference between groups for ACTH, ADH, and cortisol levels
McNamee et al. [56] (2001)	Mean VAS movement	Reduced in FNB + SNB B (0) vs IV PCA (1.5) at 8 hours only and in FNB + SNB R (0) vs IV PCA (0.5) at 4 hours only	< 0.05	2°	II	Pain score in all three groups < 2.5 mm for first 20 hours; reduced pain in B group vs R between 24 and 48 hours; all patients received spinal diamorphine
	Morphine consumption	Reduced in FNB + SNB B vs IV PCA from 8 to 48 hours	< 0.05	1°	I	
	Morphine consumption	Reduced in FNB + SNB R vs IV PCA for 24 hours	< 0.05	1°	I	

Table 6. continued

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Ng et al. [61] (2001)	Verbal pain score rest	Reduced in all groups vs IV PCA at 1, 4, 8, and 24 hours	< 0.05	2°	I	Recordings made until 48 hours; no difference between 3-in-1 FNB R 0.25%, 3-in-1 FNB R 0. 5%, or 3-in-1 FNB B 0.25% in pain scores or morphine consumption
	Verbal pain score movement	Reduced in all groups vs IV PCA at 1, 4, 8, 24, and 48 hours	< 0.05	2°	I	
	Cumulative morphine consumption	Reduced in all groups vs IV PCA at 1, 8, 24, and 48 hours	< 0.05	1°	I	
Capdevila et al. [14] (1999)	VAS rest	Decreased in CFNB and CEA vs IV PCA up to 48 hours	< 0.01	2°	II	No difference in pain scores or morphine requirements between CFNB and CEA
	VAS during CPM	Decreased in CFNB and CEA vs IV PCA up to 48 hours	< 0.01	2°	II	
Ganapathy et al. [25] (1999)	VAS rest	No difference up to 48 hours postoperatively	NS	1°	I	No difference in pain scores during activity from POD 1 up to day of discharge; significant reduction in morphine consumption between CFNB 0.2% B and placebo ($p < 0.05$) at 0-4 hours and POD 1 but not in between this period; fentanyl in spinal anesthetic in all groups
	VAS movement	Decreased pain scores on day of surgery only in CFNB 0.2% B and 0.1% B vs placebo	< 0.05			
	24-hour morphine consumption (mg)	CFNB 0.2% B (49), CFNB 0.1% B (84.6), placebo (73)	0.06			
Allen et al. [2] (1998)	VAS rest	Decreased up to 8 hours in FNB and FNB + SNB vs placebo	< 0.05	2°	I	Incomplete data beyond 8 hours; SNB did not improve analgesia compared with FNB alone
	VAS movement	No difference between groups	NS			
	Total morphine consumption up to POD 2	Decreased in FNB and FNB + SNB vs placebo	< 0.02	1°	I	
Singelyn et al. [74] (1998)	Mean VAS rest 4 hours (0–100 mm)	CFNB (32), CEA (11), IV PCA (45)	< 0.001	1°	II	All pain scores lower in CFNB and CEA compared with IV PCA over the 48-hour period
	Mean VAS rest 24 hours	CFNB (17), CEA (16), IV PCA (27)	0.04			
	Mean VAS rest 48 hours	CFNB (10), CEA (12), IV PCA (20)	0.03			
	Mean VAS movement 4 hours	CFNB (48), CEA (), IV PCA (66)	< 0.001			
	Mean VAS movement 24 hours	CFNB (36), CEA (33), IV PCA (52)	0.01			
	Mean VAS movement 48 hours	CFNB (25), CEA (30), IV PCA (42)	0.06			
Hirst et al. [35] (1996)	VAS rest	No difference at any time over 48 hours	< 0.05	1°	I	Powered to detect a minimum treatment effect of 30%; no difference in pain scores or morphine requirements beyond recovery room
	VAS movement	Decreased in FNB and CFNB vs IV PCA in recovery room only	NS			
	Morphine consumption	No difference between groups over 48 hours	NS			

Table 6. continued

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Moiniche et al. [59] (1994)	VAS rest	Decreased in CEA compared with IM opioid	0.001	1°	II	Reduced VAS in CEA group during this time
	VAS flexion	Less in CEA compared with IM opioid	0.0002			
	VAS walking	Less in CEA compared with IM opioid	0.01			
	Total morphine consumption	Less in CEA group compared with IM opioid even after discontinuing CEA	< 0.05			
Sharrock et al. [73] (1994)	VAS rest evening postoperatively	CEA (30), IV opioid (44)	NS	2°	II	Significantly greater pain scores initially in CEA group when epidural discontinued
	VAS rest POD 1	CEA (47), IV opioid (53)	NS			
	Mean fentanyl PACU	CEA (1108), IV opioid (4982)	< 0.01	2°	II	
	Mean fentanyl POD 1	CEA (722), IV opioid (3312)	< 0.01			
Edwards and Wright [18] (1992)	Mean VAS 24 hours (0–100 mm)	CFNB (25), IM opioid (56)	< 0.01	1°	II	No data beyond 24 hours
	24-hour papaveretum consumption	CFNB (15.5 mg), IM opioid (43.0 mg)	< 0.01			
Serpell et al. [70] (1991)	Mean VAS 24 hours (0–100 mm)	CFNB (32), IV PCA (40)	NS	1°	II	
	Mean VAS 48 hours (0–100 mm)	CFNB (34), IV PCA (37)	NS			
	48-hour morphine consumption (mg)	CFNB (60), IV PCA (91)	< 0.05			
Nielson et al. [63] (1990)		"No difference in the amount or choice of postoperative opioid use"		2°	II	More than 20% dropout; no sample size justification

* Results are expressed as scores on a visual analog scale (VAS) or numeric rating scale (NRS) (0–10) unless stated otherwise; p values provided where available; LoE = level of evidence; POD = postoperative day; FNB = femoral nerve block; IV = intravenous; PCA = patient-controlled analgesia; NS = not significant; CFNB = continuous femoral nerve block; CPM = continuous passive movement; CEA = continuous epidural analgesia; R = ropivicaine; DOS = day of surgery; CPB = continuous psoas block; OB = obturator nerve block; ACTH = adrenocorticotrophic hormone; ADH = antidiuretic hormone; SNB = sciatic nerve block; B = bupivicaine; PACU = postanesthesia care unit; IM = intramuscular; 1° = primary; 2° = secondary.

Table 7. General anesthesia versus regional anesthesia and/or systemic versus regional analgesia for TKA: adverse effects*

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Good et al. [28] (2007)	Nausea	FNB (4.5), placebo (0)	NS	2°	II	
	Urinary retention	FNB (9), placebo (5)	NS			
Kardash et al. [45] (2007)	Nausea DOS	FNB (26), Obturator (45), IV PCA (25)	NS	2°	II	
	Nausea 24 hours	FNB (32), Obturator (50), IV PCA (40)	NS			
	Pruritis DOS	FNB (0), Obturator (0), IV PCA (0)	NS			
	Pruritis 24 hours	FNB (0), Obturator (5), IV PCA (0)	NS			
	Sedation DOS	FNB (26), Obturator (25), IV PCA (35)	NS			
	Sedation 4 hours	FNB (11), Obturator (25), IV PCA (30)	NS			
	Urinary retention DOS	FNB (26), Obturator (40), IV PCA (20)	NS			
	Urinary retention 24 hours	FNB (16), Obturator (35), IV PCA (10)	NS			
Seet et al. [69] (2006)	PONV	CFNB 0.15% B (35), CFNB 0.2% B (44), IV PCA (70)	0.094	2°	II	Superior patient satisfaction in both CFNB groups vs IV PCA
	Pruritis	CFNB 0.15% B (24), CFNB 0.2% B (11), IV PCA (5)	0.23			
	Sedation	CFNB 0.15% B (47), CFNB 0.2% B (39), IV PCA (75)	0.059			
	Urinary retention	CFNB 0.15% B (18), CFNB 0.2% B (28), IV PCA (20)	0.777			
Chu et al. [16] (2006)	Nausea 48 hours	CEA (30), IV PCA (40)	0.42	2°	II	
	Vomiting 48 hours	CEA (33), IV PCA (23)	0.39			
	Pruritis 48 hours	CEA (10), IV PCA (20)	0.28			
	Urinary retention 48 hours	CEA (43), IV PCA (27)	0.18			
Axelsson et al. [6] (2005)	PONV	CEA 0.2% R (20), CEA 0.125% R (33), placebo (33)	NS	2°	II	
	Pruritis	CEA 0.2% R (53), CEA 0.125% R (53), placebo (0.7)	< 0.05	2°	I	
Szczukowski et al. [76] (2004)	Nausea	No difference (no data)	NS	2°	II	Sedation measured using a 5-point scale; no difference in sedation on average or on POD 2 or 3.
	Vomiting	No difference (no data)	NS		II	
	Pruritis	No difference (no data)	NS		II	
	Sedation POD 1	FNB (2.26), sham + IV PCA (2.67)	0.045		I	
	Urinary retention	No difference (no data)	NS		II	
Farag et al. [21] (2005)	Sedation POD 1	CEA (3.8), IV PCA (5.3)	0.04	2°	II	Sedation measured using 10-point verbal scale; urinary catheter removed from both groups on POD 1 and episodes of urinary retention recorded thereafter
	Sedation POD 2	CEA (2.9), IV PCA (3.5)	NS			
	Urinary retention	CEA (0), IV PCA (0)	NS			
Macalou et al. [50] (2004)	Nausea 6 hours	FNB (34), FNB + OB (12), IV PCA (46)	0.0117	2°	I	
	Vomiting 6 hours	FNB (7), FNB + OB (6), IV PCA (39)	NS	2°	II	
	Sedation 6 hours	FNB (7), FNB + OB (15), IV PCA (39)	NS	2°	II	
Adams et al. [1] (2002)	Nausea	FNB (29), CEA (57), IV PCA (38)	NS	2°	II	
	Vomiting	FNB (14), CEA (24), IV PCA (29)	NS			

Table 7. continued

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Wang et al. [79] (2002)	Overall opioid-related adverse effects	FNB (5), placebo (54)	0.014	2°	I	Defined as hypotension, respiratory depression, sedation, urinary retention or nausea and vomiting
McNamee et al. [56] (2001)	Emesis score	Less in FNB + SNB B vs IV PCA group at 8 hours only	< 0.05	2°	I	Observations continued for 48 hours
	Sedation	No difference between groups	NS	2°	II	
Ng et al. [61] (2001)	Nausea	No difference between groups	NS	2°	II	
	Vomiting	No difference between groups	NS			
	Pruritis	No difference between groups	NS			
	Sedation	No difference between groups	NS			
Capdevila et al. [14] (1999)	Nausea 24 hours	CFNB (5),† CEA (12), IV PCA (21)	< 0.05	2°	II	Observations continued for 72 hours; no significant differences beyond times stated; urinary retention only significantly different in recovery room
	Vomiting 24 hours	CFNB (0), CEA (6), IV PCA (10)	NS			
	Pruritis 24 hours	CFNB (0), CEA (6), IV PCA (10)	NS			
	Sedation 24 hours	CFNB (10), CEA (6), IV PCA (16)	NS			
	Urinary retention	CFNB (0), CEA (53),†,‡ IV PCA (21)	< 0.05			
Ganapathy et al. [25] (1999)	PONV	No difference between groups	NS	2°	II	
Allen et al. [2] (1998)	Nausea 4 hours	FNB (17), FNB + SNB (33), IV PCA (50)	NS	2°	II	Trend toward worse in PCA group; no difference in patient satisfaction
	Nausea POD 1	FNB (25), FNB + SNB (42), IV PCA (25)	NS			
	Pruritis 4 hours	FNB (0), FNB + SNB (17), IV PCA (17)	NS			
	Pruritis POD 1	FNB (0), FNB + SNB (0), IV PCA (17)	NS			
	Sedation 4 hours	FNB (17), FNB + SNB (0), IV PCA (50)	NS			
	Sedation POD 1	FNB (0), FNB + SNB (0), IV PCA (8)	NS			
Singelyn et al. [74] (1998)	PONV	CFNB (33), CEA (27), IV PCA (40)	0.74	2°	II	†
	Urinary retention	CFNB (0), CEA (40),† IV PCA (13)	0.05			
Hirst et al. [35] (1996)	Nausea 24 hours	FNB (45), CFNB (36), IV PCA (91)	NS	2°	II	No difference in patient satisfaction
	Nausea 48 hours	FNB (9), CFNB (9), IV PCA (36)	NS			
Serpell et al. [70] (1991)	Nausea	CFNB (69), IV PCA (75)	NS	2°	II	No difference in antiemetic doses between groups
	Vomiting	CFNB (54), IV PCA (50)	NS			

* Results are expressed as percentage of incidence unless stated otherwise; †vs IV PCA; ‡vs CFNB; p values provided where available; LoE = level of evidence; FNB = femoral nerve block; NS = not significant; DOS = day of surgery; IV = intravenous; PCA = patient-controlled analgesia; PONV = postoperative nausea and vomiting; CFNB = continuous femoral nerve block; B = bupivicaine; CEA = continuous epidural analgesia; R = ropivicaine; POD = postoperative day; OB = obturator nerve block; SNB = sciatic nerve block; 1° = primary; 2° = secondary.

6 hours postoperatively compared with systemic analgesia. All patients, however, whether they had THA or TKA, were analyzed in aggregate as one group despite important differences in the severity of postoperative pain between these two surgical procedures. In contrast, we found when TKA is examined independently, pain scores frequently were reduced for up to 48 hours. As may be expected, this analgesic benefit was most evident when continuous catheter techniques were used, whether epidural or peripheral perineural techniques.

We did not aim to determine the ideal choice of RA technique for TKA. A recently published meta-analysis concluded CPNB is superior to epidural anesthesia for TKA [23]. Another systematic review also addressed this issue [22]. Furthermore, our search criteria did not extend to examining whether addition of a sciatic or other nerve

Table 8. General anesthesia versus regional anesthesia and/or systemic versus regional analgesia for TKA: length of stay*

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Kardash et al. [45] (2007)	Mean hospital stay	FNB (6.2), Obturator (6.7), IV PCA (6.1)	NS	2°	II	
Seet et al. [69] (2006)	Median hospital stay	CFNB 0.15%B (6), CFNB 0.2% B (7), IV PCA (7)	0.461	2°	II	
Chu et al. [16] (2006)	Median hospital stay	EA (7.5), GA (9)	0.32	2°	II	
Tugay et al. [77] (2006)	Length of stay	No difference (no data)	NS	2°	II	
Szczukowski et al. [76] (2004)	Length of stay	No difference (no data)	NS	2°	II	
Wang et al. [79] (2002)	Hospital stay	FNB (3), placebo (4)	< 0.05	2°	I	Early discharge defined as discharge before POD 3
	Early discharge (% of patients)	FNB (26.7), placebo (6.7%)	< 0.1			
Ng et al. [61] (2001)	Mean length of stay	3-in-1 FNB R 0.25% (9.5), 3-in-1 FNB R 0.5% (9.3), 3-in-1 FNB B 0.25% (9.3), IV PCA (8.8)	NS	2°	II	
Capdevila et al. [14] (1999)	Length of stay in rehabilitation facility	CFNB (40), CEA (37), IV PCA (50)	< 0.05	2°	II	
Singelyn et al. [74] (1998)	Total length of stay	CFNB (17), CEA (16), IV PCA (21)	< 0.001	2°	II	Duration of stay included hospital and rehabilitation phases of recovery
Williams-Russo et al. [83] (1995)	Mean hospital stay	EA (12.7), GA (12.7)	NS	2°	II	
Moiniche et al. [59] (1994)	Median hospital stay	EA (12), GA (13)	NS	2°	II	
Sharrock et al. [73] (1994)	Mean length of stay	CEA (16.7), IV opioid (15.6)	NS	2°	II	
Mitchell et al. [57] (1991)	Hospital stay	EA (10.4), GA (11.0)	NS	2°	II	

* Results are expressed as days unless stated otherwise; p values provided where available; LoE = level of evidence; FNB = femoral nerve block; IV = intravenous; PCA = patient-controlled analgesia; NS = not significant; CFNB = continuous femoral nerve block; EA = epidural anesthesia; GA = general anesthesia; R = ropivicaine; B = bupivicaine; CEA = continuous epidural analgesia; 1° = primary; 2° = secondary.

block to FNB is beneficial; this subject remains a matter of controversy in the anesthetic literature [60].

Like postoperative pain, opioid-related adverse effects, especially nausea and vomiting, are a major concern to patients and can delay discharge from the hospital [51, 66]. We found Level I evidence that FNB, either alone or in combination with obturator or sciatic block, reduced opioid-related side effects. In general, a reduction in morphine consumption with RA was not always associated with a reduction in adverse effects, but this may be the result of inadequate powering. The 10 RCTs in which no benefit was observed were graded as Level II. These were either inadequately powered or had poor methodologic quality.

Although no difference in cognitive defects was observed between GA and RA, intravenous sedation was administered to the RA groups in both studies and this could have influenced results. In a separate well-conducted trial that examined patients who had THAs and patients who had TKAs as one population (and therefore was not considered in our review), there was no long-term cognitive difference between the RA and GA groups [40].

RA and regional analgesia may shorten length of stay in the hospital and hasten postoperative rehabilitation, which potentially could have important economic benefits. Although epidural analgesia and CFNB for TKA each can facilitate rehabilitation, CFNB generally is preferred, because bilateral blockade, hypotension, pruritis, bradycardia, and nausea and vomiting are avoided whereas the patient's anticoagulation status is arguably less of a concern [6, 8, 14, 17, 32, 36, 74, 85]. However, in two of the three trials showing a reduced length of stay with RA compared with systemic analgesia, the hospital and rehabilitation center stays were longer than current practice [14, 74]. As managed clinical pathways and shorter hospital stays become increasingly prominent after TKA, so too may the role of RA. However, with short, protocolized inpatient visits and multiple confounding factors influencing discharge time, it is becoming more difficult to show reduced lengths of stay with RA [38, 68]. Reports of TKAs facilitated by ambulatory CFNB catheters at home have been published and may populate the literature in the near future [37, 38].

In conclusion, we found insufficient evidence from RCTs alone to conclude if anesthetic technique influenced mortality, cardiovascular morbidity other than postoperative hypotension, or the incidence of DVT and PE in the setting

Table 9. General anesthesia versus regional anesthesia and/or systemic versus regional analgesia for TKA: rehabilitation*

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Good et al. [28] (2007)	Knee flexion POD 2	FNB (55), placebo (55)	NS	2°	II	
	Knee flexion POD 3	FNB (60), placebo (64)	NS			
	Knee extension POD 2	FNB (−14), placebo (–15)	NS			
	Knee extension POD 3	FNB (–12.5), placebo (–15)	NS			
	Ambulation distance	No difference between groups on POD 1, 2, or 3	NS			
Kardash et al. [45] (2007)	Knee flexion POD 2	FNB (60), Obturator (62), IV PCA (55)	NS	2°	II	
	Knee flexion discharge	FNB (65), Obturator (73), IV PCA (72)	NS			
Seet et al. [69] (2006)	Median time first ambulation (hours)	CFNB 0.15% R (64), CFNB 0.2% R (65.7), IV PCA (59.5)	0.954	2°	II	
Chu et al. [16] (2006)	Median time to 10 steps (days)	EA (6), IV PCA (7)	0.06	2°	II	
Tugay et al. [77] (2006)	Functional Level Test	No difference at POD 2 or discharge (no data)	NS	2°	II	Functional Level Test measured assistance required for transferring, ambulating, and climbing stairs; no difference in ambulation speed test between groups
Axelsson et al. [6] (2005)	Mobilization	No difference at 24 or 48 hours between groups	NS	2°	II	Mobilization defined as ability sit out of bed and walk 3–4 m aided by walker and nurse; 27% of placebo group unable to mobilize at 24 hours because of pain; 27% of 0.2% R group unable to mobilize because of leg weakness
Szczukowski et al. [76] (2004)	Knee ROM discharge	No difference (no data)	NS	2°	II	
	Distance ambulated POD 1, 2, 3	No difference (no data)	NS	2°	II	
Wang et al. [79] (2002)	Knee flexion POD 2	FNB (70), placebo (60)	< 0.05	2°	I	Ambulation goals were a fixed distance on each POD
	Knee flexion discharge	FNB (76.7), placebo (71)	0.09			
	Ambulation goals achieved POD 1 (% patients)	FNB (93.3), placebo (46.7)	< 0.05	2°		
	Ambulation goals achieved POD 2, 3	Superior in FNB	< 0.05			

Table 9. continued

Study (year)	End point	Results	p Value	Outcome	LoE	Remarks
Capdevila et al. [14] (1999)	Knee flexion POD 1	CFNB (40), CEA (45), IV PCA (30)†	< 0.05	1°	II	No difference in knee flexion at 1 and 3 months CFNB and CEA groups consistently met rehabilitation goals
	Knee flexion POD 5	CFNB (80), CEA (85), IV PCA (60)†	< 0.05			
	Knee flexion discharge	CFNB (90), CEA (90), IV PCA (80)†	< 0.05			
Ganapathy et al. [25] (1999)	ROM POD 1	Increased in CFNB 0.2% B vs placebo	< 0.05	2°	I	No difference in ROM between groups after POD 1 until POD 3 and at 6 week assessment
Singelyn et al. [74] (1998)	Knee flexion POD 1	CFNB (56), CEA (48), IV PCA (33)	0.009	2°	II	No difference in knee flexion between CFNB and CEA at any time
	Knee flexion POD 10	CFNB (88), CEA (91), IV PCA (77)	< 0.001			
	Knee flexion 6 weeks	CFNB (116), CEA (114), IV PCA (103)	0.03			
	Knee flexion 3 months	CFNB (124), CEA (121), IV PCA (116)	0.22			
	Mean time first ambulation (days)	CFNB (3.5), CEA (3.5), IV PCA (4.3)	0.02			
Williams-Russo et al. [82] (1996)	Mean time to 90° flexion (days)	EA (6.9), GA (7.8)	< 0.03	1°	II	No difference in all other functional milestones: unassisted ($p = 0.44$) or assisted transfer ($p = 0.73$), unassisted ($p = 0.4$) or assisted ($p = 0.75$) walker, unassisted ($p = 0.26$) or assisted ($p = 0.56$) cane
	Mean time to assisted stair climbing (days)	EA (7.9), GA (9.5)	< 0.01			
Moiniche et al. [59] (1994)	Hours of ambulation	No difference between groups at 0–48 hours or 48-hour discharge	0.22	2°	II	No difference between groups in activity scores ($p = 0.09$) based on dependence on nurses for sanitation, meals, dressing, and mobilization
Sharrock et al. [73] (1994)	Percentage who achieved 90° knee flexion	CEA (81), IV opioid (76)	NS	2°	II	No difference in other rehabilitation outcomes (transfer, stairs unassisted)
	Day walking unassisted	CEA (10.4), IV opioid (8.6)	NS	2°	II	

* Results are expressed as mean knee flexion and extension (degrees) unless stated otherwise; †vs CFNB and CEA; p values provided where available; LoE = level of evidence; POD = postoperative day; FNB = femoral nerve block; NS = not significant; IV = intravenous; PCA = patient-controlled analgesia; CFNB = continuous femoral nerve block; R = ropivicaine; EA = epidural anesthesia; ROM = range of motion; CEA = continuous epidural analgesia; B = bupivicaine; GA = general anesthesia; 1° = primary; 2° = secondary.

of routine thromboprophylaxis. Our systematic review does not suggest a difference in blood loss or duration of surgery in patients receiving GA and/or systemic analgesia versus RA and/or RA for TKA. However, RA does reduce postoperative pain and opioid-related adverse effects for TKA. Length of stay also may be reduced and rehabilitation facilitated by RA compared with GA.

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