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SYMPOSIUM: PERIOPERATIVE PAIN MANAGEMENT IN ORTHOPAEDIC SURGERY

The Influence of Anesthesia and Pain Management on Cognitive Dysfunction After Joint Arthroplasty

A Systematic Review

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Abstract

Background Despite the overall success of total joint arthroplasty, patients undergoing this procedure remain susceptible to cognitive decline and/or delirium, collectively termed postoperative cognitive dysfunction. However, no consensus exists as to whether general or regional anesthesia results in a lower likelihood that a patient may experience this complication, and controversy surrounds the role of pain management strategies to minimize the incidence of postoperative cognitive dysfunction.

Questions/purposes We systematically reviewed the English-language literature to assess the influence of the following anesthetic and/or pain management strategies on the risk for postoperative cognitive dysfunction in patients undergoing elective joint arthroplasty: (1) general versus regional anesthesia, (2) different parenteral, neuraxial, or inhaled agents within a given type of anesthetic (general or regional), (3) multimodal anesthetic techniques, and (4) different postoperative pain management regimens.

Methods A systematic search was performed of the MEDLINE® and EMBASE™ databases to identify all studies that assessed the influence of anesthetic and/or pain management strategies on the risk for postoperative cognitive dysfunction after elective joint arthroplasty. Twenty-eight studies were included in the final review, of which 21 (75%) were randomized controlled (Level I) trials, two (7%) were prospective comparative (Level II) studies, two (7%) used a case-control (Level III) design, and three (11%) used retrospective comparative (Level III) methodology.

Results The evidence published to date suggests that general anesthesia may be associated with increased risk of early postoperative cognitive dysfunction in the early postoperative period as compared to regional anesthesia, although this effect was not seen beyond 7 days. Optimization of depth of general anesthesia with comprehensive intraoperative cerebral monitoring may be beneficial, although evidence is equivocal. Multimodal anesthesia protocols have not been definitively demonstrated to reduce the incidence of postoperative cognitive dysfunction. Nonopioid postoperative pain management techniques, limiting narcotics to oral formulations and avoiding morphine, appear to reduce the risk of postoperative cognitive dysfunction.

Conclusions Both anesthetic and pain management strategies appear to influence the risk of early cognitive

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dysfunction after elective joint arthroplasty, although only one study identified differences that persisted beyond 1 week after surgery. Investigators should strive to use accepted, validated tools for the assessment of postoperative cognitive dysfunction and to carefully report details of the anesthetic and analgesic techniques used in future studies.

Introduction

Total joint arthroplasty remains among the most successful contemporary surgical interventions. Due in part to advances in preoperative medical optimization and evidence-based clinical care pathways, notwithstanding the substantial invasiveness of arthroplasty procedures, the incidence of major medical and surgical complications after elective joint arthroplasty remains low, with reported 30-day mortality rates of around 0.2% [30]. Despite these efforts, however, patients undergoing total joint arthroplasty remain susceptible to postoperative cognitive decline and/or delirium, with reported rates ranging from 7% to 75%, depending on the definition, patient population, and assessment tools used [11, 37]. These adverse events can result in delayed mobilization and discharge from hospital, long-term cognitive dysfunction, and potentially increased rates of return to hospital and mortality [42]. As a result, postoperative cognitive dysfunction can have a significant impact on both health resource utilization and patients' health-related quality of life.

The etiology of postoperative cognitive dysfunction is multifactorial, with a number of nonmodifiable factors reported to influence the incidence, including major surgery, older age, and preexisting cognitive impairment (Table 1) [10, 21]. A number of modifiable factors also have been reported by investigators, including the quality of perioperative pain control and quantity and classes of medications used [10]. However, no consensus exists concerning the optimal choice of anesthetic and pain management strategies to minimize the incidence of postoperative cognitive dysfunction in surgical patients.

Given this, we systematically reviewed the English-language literature to assess the influence of anesthetic and/or pain management strategies on the risk for postoperative cognitive dysfunction in patients undergoing elective joint arthroplasty. Specifically, we determined whether the risks of these conditions are affected by the use of (1) general as compared to regional anesthesia, (2) different parenteral, neuraxial, or inhaled agents within a given type of anesthetic (general or regional), (3) multimodal anesthetic techniques, and (4) different postoperative pain management regimens.

Table 1. Predisposing and precipitating factors reported to be associated with delirium and/or postoperative cognitive dysfunction in hospitalized patients [10, 21]

Factor
Predisposing
Increased age
Male sex
Preexisting cognitive impairment
Previous delirium
Immobility
Sensory impairment (auditory, visual)
Decreased oral intake
Polypharmacy
Narcotic or benzodiazepine use
Excessive alcohol intake
Tobacco use
Trauma
Severe illness
Precipitating
Anticholinergic drugs
Benzodiazepines
Primary intracranial neurologic disease
Infection
Iatrogenic complications
Shock
Hypoxia
Fever
Hypothermia
Dehydration
Poor nutritional status
Metabolic abnormalities
Anemia
Surgery
Intensive care unit admission
Urinary catheter use
Use of restraints
Acute pain
Sleep deprivation

Search Criteria and Strategy

Eligibility Criteria

Original studies comparing the effect of different anesthetic and/or pain management strategies on the risk of postoperative cognitive dysfunction after elective joint arthroplasty were deemed eligible for review. Anesthetic and/or pain management strategies were defined as any combination of oral, parenteral, inhaled, and/or regional medications administered immediately before induction of anesthesia, during the

surgical procedure, or after surgery but before discharge from hospital. Different types of anesthesia (eg, general, neuraxial, regional) were considered to be different anesthetic strategies for the purposes of this review. Postoperative cognitive dysfunction was defined as encompassing any acute change in neurocognitive status after surgery, including postoperative cognitive decline, delirium, or confusion. With the exception of dementia, no specific limitations were applied to the type or magnitude of postoperative cognitive dysfunction considered eligible for inclusion in the present review. Any studies that included either (1) only patients who underwent elective major joint arthroplasty (specifically, hip, knee, shoulder, elbow, or ankle) or (2) patients who underwent any of a number of different surgical procedures including elective orthopaedic surgery requiring hospitalization were deemed eligible for inclusion. Only comparative studies including at least two different pain management strategies, irrespective of study design, were deemed eligible. Case series assessing the incidence of postoperative cognitive dysfunction with a single pain management strategy were excluded. Review articles, published abstracts, letters to the editor, study protocols, case reports (defined as studies encompassing < 10 patients), and reports without English full-text versions were similarly excluded.

Information Sources and Search

An electronic search was performed, in duplicate, of the Ovid MEDLINE® and EMBASE™ databases to identify all studies published up to March 2013 assessing the effect of anesthetic and/or pain management strategies on postoperative cognitive dysfunction. Any disagreements were resolved by consensus discussion among the authors. The following search string was used to query citation titles and abstracts: "(delirium or cognitive or cognition or confusion or confused) and (pain management or anesthesia or anaesthesia or anesthetic or anaesthetic or spinal or epidural or multimodal or pain control) and (arthroplasty or joint replacement or elective joint or orthopaedic or orthopedic or non-cardiac or non cardiac)." A second search of the same databases was performed using the following search string, limited to MeSH headings: "(pain management or anesthesia) and orthopedic procedures and (delirium or postoperative complications)." The two searches yielded 592 records when combined using the OR operator, with 445 remaining after automated deduplication. A flow diagram of the search process is shown (Fig. 1).

Study Selection

Citation records were extracted to spreadsheet software and sorted by metadata tags. We excluded 178 records deemed to not meet our eligibility criteria based on publication type metadata, including 79 review articles, 65 published abstracts, 14 case reports, 11 reports without full-text versions in English, four editorials, three letters to the editor, one note, and one book chapter. The remaining 267 records were sorted by title and manually screened for duplicate studies, with six duplicate citations identified and removed. The remaining records were screened by title and publication type. Any studies that definitely did not meet eligibility criteria were discarded, with 162 records excluded for the following reasons: nonapplicable content ($n = 152$) and no full-text English version available ($n = 10$). Full-text versions of the remaining 99 records, which had been judged to be either probably relevant or of unknown relevance, were obtained. These were screened and/or read by two reviewers (MGZ, RG) to identify those studies that definitely met the inclusion criteria for this review. Seventy-one records were found to be ineligible after screening and were excluded, leaving 28 studies in the final review [2–4, 7, 12, 14–20, 24, 26, 27, 29, 33–36, 38, 39, 41, 44–48].

Data Collection

Data from the included studies were extracted to spreadsheet software for analysis. The specific information extracted included the following: (1) study details, including study design and level of evidence; (2) study population details, including number of patients and their mean age (range), any reported inclusion/exclusion criteria, and the surgical procedures performed; (3) details of pain management strategies, including type of anesthesia and analgesic and/or anesthetic medications given including route and dosing, when applicable; and (4) details of assessment of postoperative cognitive dysfunction, including assessment tools, time point and frequency of assessment(s), and reported incidence of postoperative cognitive dysfunction at various time points. In cases where rates and proportions of postoperative cognitive dysfunction were given but no statistical comparison was provided, p values were calculated using the chi-square statistic.

Study Designs and Populations

The large majority of studies identified (21 of 28, 75%) used a prospective randomized design to compare the effects of pain management strategies on postoperative cognitive dysfunction. However, of those studies, only nine of 21 (43%) explicitly reported blinding of patients, clinicians, and/or assessors to the participants' treatment arm allocation [4, 12, 15, 20, 24, 27, 29, 47, 48]. Only nine of 21 (43%) reported performing an a priori power calculation

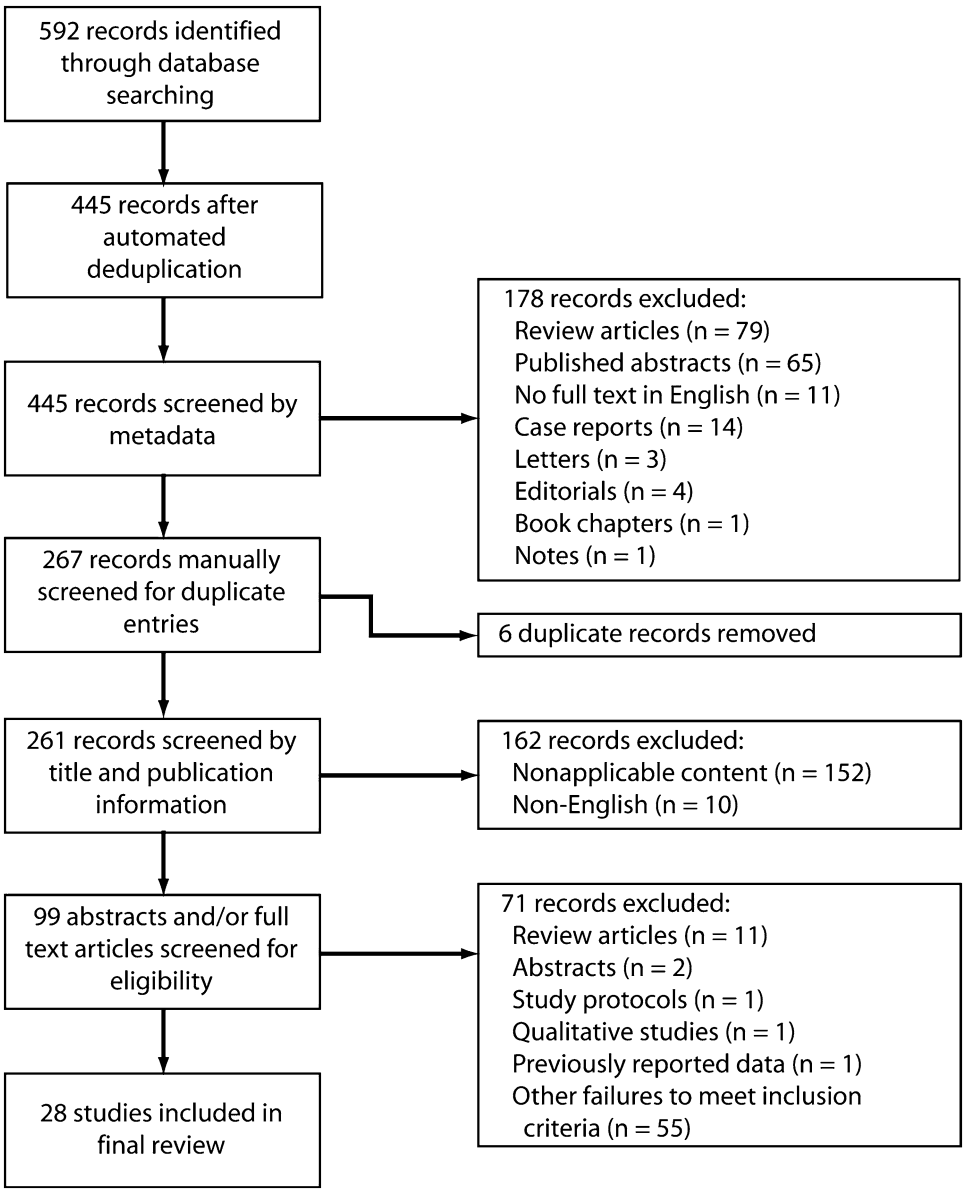

Fig. 1 A flow diagram illustrates the systematic search process used to identify the studies included in the final review.

for the outcome of postoperative cognitive dysfunction [4, 16, 24, 27, 29, 34, 38, 39, 48], with one of these studies failing to recruit a sufficient number of patients [38]. Of the remaining seven studies, two used a prospective comparative design [2, 41], two used a case-control design [33, 44], and three used a retrospective comparative design [17, 19, 36].

Nineteen studies encompassing 2824 patients were limited to those who had undergone elective total joint arthroplasty only. This included eight studies of patients who underwent either TKA or THA [7, 12, 17, 18, 20, 24, 36, 47], eight studies of patients who underwent unilateral TKA [15, 19, 26, 35, 39, 41, 45, 48], two studies of patients who underwent unilateral THA [16, 34], and one study of patients who underwent bilateral TKA [46]. The remaining nine studies encompassing 2426 patients investigated postoperative cognitive dysfunction in a mixed major noncardiac surgical population, which included patients who underwent elective joint arthroplasty.

A range of definitions and assessment tools for postoperative cognitive dysfunction were reported. Eleven studies assessed postoperative cognitive dysfunction using multiple validated neuropsychologic and/or cognitive tests [2, 4, 14, 24, 29, 35, 38, 41, 44, 45, 47]. Eleven studies assessed either cognitive dysfunction or confusion without specifying diagnostic criteria [7, 15–20, 27, 34, 36, 48]. Five studies assessed postoperative cognitive dysfunction using either the Confusion Assessment Method, which has been validated for delirium screening [22], or the *Diagnostic and Statistical Manual of Mental Disorders* [1] criteria for

delirium [4, 26, 29, 33, 46]. Four studies assessed postoperative cognitive dysfunction by an observed change in scores on the Mini Mental Status Examination [4, 12, 18, 47], while two assessed for change on the Wechsler Adult Intelligence Scale [3, 35].

Results

The Use of General Versus Regional Anesthesia

The studies reported to date suggest that general anesthesia may be associated with increased cognitive dysfunction in the early postoperative period, although any differences appear to resolve within the first week after surgery (Table 2). Nine studies were identified that compared the incidence of postoperative cognitive dysfunction after general versus regional anesthesia. Three studies reported worse cognitive function and/or confusion in patients who had undergone surgery under general anesthesia between 1 and 7 days after surgery [3, 26, 38]. One of these studies limited assessment times to a maximum of 3 days postoperatively [3], while the other two found no differences in cognitive function at the second postoperative assessment (Postoperative Day 2 and 3 months after surgery, respectively). In the remaining six studies that failed to find any difference in cognitive function based on type of anesthesia [2, 14, 24, 35, 41, 45], the first postoperative assessment ranged from 1 week to 3 months after surgery, suggesting that any differences that may have been present immediately after surgery had resolved before the first evaluation. Overall, the available evidence suggests that general anesthesia may be associated with an increased risk of postoperative cognitive dysfunction in the immediate postoperative period. However, this effect appears to be transient, with no data suggesting that these differences are maintained more than 1 week after surgery.

The Use of Different Anesthetic and/or Analgesic Techniques Within a Given Type of Anesthesia

Optimization of depth of general anesthesia with comprehensive intraoperative cerebral monitoring may be beneficial, although the quantity of evidence on this question and other related questions is limited, and the effect sizes—where effects were observed—generally were small. Four studies investigated the impact of differences in general anesthetic technique on the incidence and/or severity of postoperative cognitive dysfunction (Table 3). The factors studied included the use of intraoperative cerebral monitoring ($n = 3$) and use of nitrous oxide ($n = 1$). Wong et al. [47] reported that maintenance of anesthesia using EEG monitoring was associated with faster time to orientation in the recovery room but no difference in daily psychometric test results up to Postoperative Day 3. Similarly, Steinmetz et al. [44] found no difference in depth of anesthesia as tracked using EEG monitoring between patients who did and did not have postoperative cognitive dysfunction at 1 week after surgery. In contrast, Ballard et al. [4] found that patients who had depth of anesthesia optimized using both EEG and regional brain oxygenation monitoring had differences in postoperative cognitive dysfunction up to final followup time of 52 weeks. However, none of these studies assessed the effectiveness of cerebral monitoring stratified by potential risk factors for cognitive dysfunction. The final study suggested that the incidence of postoperative cognitive dysfunction was not affected by the use of inhaled nitrous oxide for the maintenance of anesthesia [29].

Two studies assessed differences in techniques for spinal anesthesia but failed to show any difference in postoperative cognitive dysfunction in either case [12, 39]. Specifically, both the addition of intrathecal clonidine and the maintenance of sedation with inhaled xenon as compared to intravenous (IV) propofol did not have an effect on the development of postoperative cognitive dysfunction.

Multimodal Anesthetic Techniques

Overall, the retrospective comparative designs, variability in anesthetic and analgesic regimens, and limited number of patients in the few studies that investigated this question precluded the assessment of the impact of multimodal protocols on the risk for postoperative cognitive dysfunction after elective joint arthroplasty. Only two studies were identified that assessed the impact of multimodal anesthesia on postoperative cognitive dysfunction, with equivocal findings (Table 4). Hebl et al. [17] compared the use of a multimodal pathway that emphasized the use of lumbar plexus and/or femoral nerve catheters for postoperative perineural anesthesia to historical controls. While the authors identified a greater incidence of postoperative cognitive dysfunction in the control group (15% versus 0%; $p < 0.01$), both the diagnostic criteria for postoperative cognitive dysfunction and the anesthetic and analgesic regimes used in the control group were not clearly reported, complicating interpretation of the findings. In contrast, Peters et al. [36] compared a multimodal protocol emphasizing the use of periarticular intraoperative injection + long-acting oral narcotics to a historical control group that received IV patient-controlled analgesia (PCA) and found a numerically higher incidence of confusion in the multimodal group (8% versus 4%). However, the diagnostic criteria for confusion were not specified, and the study was not specifically powered to detect a difference in postoperative cognitive dysfunction.

Table 2. Studies comparing the incidence of POCD with general versus regional anesthesia

Study	Year	Study group	Age (years)*	General anesthesia		Regional anesthesia			Cognitive variables evaluated	Assessment time	Difference found?	Time point of latest significant difference	Time point of earliest similar incidence
				Medications used	Number of patients	Technique	Medications used	Number of patients					
Prospective randomized controlled studies													
Jones et al. [24]	1990	TKA, THA	NR (60+)	Diazepam, thiopental, pancuronium, N2O, halothane, fentanyl	72	Spinal	Bupivicaine, midazolam	74	Neuropsychologic tests	3 months	No		3 months
Prospective randomized studies													
Anwer et al. [3]	2006	Noncardiac major surgery	62 (60–64)	Midazolam, thiopental, halothane, N2O	30	Spinal or epidural	Bupivicaine or lidocaine; midazolam	30	WAIS-R	Preop 1 day 3 days	Yes	3 days (greater POCD in GA)	
Kudoh et al. [26]	2004	TKA	75 (NR)	Fentanyl, propofol, vecuroniom	75	Spinal + LMA	Bupivicaine; propofol	75	Confusion (CAM)	POD 1, 2, 3, 4	Yes	1 day (greater POCD in GA)	2 days
Rasmussen et al. [38]	2003	Noncardiac major surgery	71 (61–84)	Variable	217	Spinal or epidural	Variable	211	Neuropsychologic tests	Preop 7 days 3 months	Yes	7 days (greater POCD in GA)	3 months
Williams-Russo et al. [45]	1995	TKA	69 (NR)	Thiopental, fentanyl, vecuronium, isflurane, N2O	128	Epidural	Lidocaine or bupivicaine, midazolam, fentanyl	134	Neuropsychologic tests Clinical delirium	Preop 1 week 6 months	No		1 week
Nielson et al. [35]	1990	TKA	60–86	Thiopental, succinylcholine, N2O, isoflurane, fentanyl	39	Spinal	Tetracaine or bupivicaine	25	WAIS Wechsler Memory Scale Neuropsychologic tests Sickness Impact Profile	Preop 3 months	No		3 months
Ghoneim et al. [14]	1988	Noncardiac major surgery	61 (25–86)	Diazepam, thiopental, isoflurane or enflurane, N2O; variable use of fentanyl	53	Spinal (38), epidural (14)	Tetracaine (spinal) or bupivicaine (epidural); variable use of diazepam, midazolam, fentanyl	52	Neuropsychologic tests	Preop 1st outpatient visit 3 months	No		1st outpatient followup
Prospective comparative studies													
Rodriguez et al. [41]	2005	TKA	69 (45–82)	Fentanyl, midazolam, propofol, atracurium, sufentanil, sevoflurane, N2O	12	Spinal	Midazolam; neuraxial agent NR	25	Neuropsychologic tests	Preop 1 week 3 months	No		1 week
Ancelin et al. [2]	2001	Orthopaedic elective	73 (64–87)	Variable	52	Regional (variable)	Variable	88	Neuropsychologic tests	Preop 9 days 3 months	No		

* Values are expressed as mean, with range in parentheses; POCD = postoperative cognitive dysfunction; NR = not reported; N2O = nitrous oxide; LMA = laryngeal mask airway; WAIS-R = Weschler Adult Intelligence Scale, revised form; CAM = Confusion Assessment Method; WAIS = Weschler Adult Intelligence Scale; preop = preoperatively; POD = postoperative day; GA = general anesthesia.

Table 3. Studies comparing the effects of different techniques within a given type of anesthesia on POCD

Study	Year	Study group	Age (years)*	Anesthetic type	Group 1		Group 2		Variables evaluated	Assessment time	Difference found?	Findings
					Intervention/ characteristic	Number of patients	Intervention/ characteristic	Number of patients				
Prospective randomized blinded studies												
Ballard et al. [4]	2012	Noncardiac major surgery	75 (72–81)	GA	EEG and regional brain oxygenation monitoring	34	Typical protocol, no advanced monitoring	38	MMSE CAM Neuropsychologic tests	Preop 1 week 12 weeks 52 weeks	Yes	Decreased mild cognitive decline at all time points ($p = 0.018$ at 1 week, $p = 0.02$ at 12 weeks, $p = 0.015$ at 52 weeks)
Leung et al. [29]	2006	Noncardiac major surgery	74 (65–95)	GA	N2O and O2 maintenance	105	O2 maintenance	105	CAM neuropsychologic tests	POD 1, 2	No	No difference in delirium (41.9% vs 43.8%) or cognitive decline (14.8% vs 18.6%)
Wong et al. [47]	2002	TKA, THA	71 (NR)	GA	EEG monitoring	29	Typical protocol, no advanced monitoring	31	MMSE Neuropsychologic tests Clinical confusion	30, 60, 120 minutes 24,48,72 hours	No	No difference in neuropsychological tests (p values not reported)
Fernandez-Galinski et al. [12]	2005	TKA, THA	75 (70–88)	Spinal	4 mg bupivicaine 15 μg fentanyl 15 μg clonidine	31	6.25 mg bupivicaine 25 μg fentanyl	30	MMSE	On arrival to recovery room	No	No difference in MMSE change between groups ($p = 0.957$)
Prospective randomized studies												
Rasmussen et al. [39]	2006	TKA	71 (NR)	Spinal	65% xenon	20	Propofol infusion	16	ISPOCD cognitive tests	Preop At discharge 10–14 weeks	No	Similar incidence of cognitive decline at discharge ($p = 0.88$) and 3-month followup ($p = 0.77$)

Table 3. continued

Study	Year	Study group	Age (years)*	Anesthetic type	Group 1		Group 2		Variables evaluated	Assessment time	Difference found?	Findings
					Intervention/ characteristic	Number of patients	Intervention/ characteristic	Number of patients				
Case-control studies												
Steinmetz et al. [44]	2010	Noncardiac major surgery	68 (61–83)	GA with EEG monitoring	POCD positive	9	POCD negative	56	Neuropsychologic tests	Preop 1 week	No	No difference in depth of anesthesia (time spent at different depths) between patients who did and did not develop POCD (specific values not reported)

* Values are expressed as mean, with range in parentheses; POCD = postoperative cognitive dysfunction; NR = not reported; GA = general anesthesia; N2O = nitrous oxide; O2 = oxygen; CAM = Confusion Assessment Method; MMSE = Mini Mental Status Examination; ISPOCD = International Study on Postoperative Cognitive Dysfunction; preop = preoperatively.

Postoperative Pain Management Strategies

In general, the findings suggest that pain management strategies that minimize the use of narcotics postoperatively have a beneficial effect on early postoperative cognitive dysfunction. Twelve studies were identified that compared the effect of different postoperative pain management strategies on the risk for postoperative cognitive dysfunction (Table 5). Langford et al. [27] reported decreased postoperative cognitive dysfunction on Postoperative Day 2 (1.8% versus 5%; $p = 0.006$) with the use of standing IV parecoxib as compared to placebo. YaDeau et al. [48] reported decreased postoperative cognitive dysfunction in patients who received a single-shot femoral nerve block immediately before TKA (2.5% versus 0%), while Marino et al. [34] found decreased postoperative cognitive dysfunction with the use of continuous lumbar or femoral block as compared to IV PCA alone (0%, 1.3%, and 10.7%, respectively). In contrast, intraarticular infusion of bupivacaine after TKA was not found to change the incidence of postoperative cognitive dysfunction as compared to placebo [15].

When narcotic medications were used, morphine and meperidine appeared to be associated with an increased risk of postoperative cognitive dysfunction, irrespective of the mode of administration (IV, intramuscular [IM], or epidural). Inan et al. [20] found no difference in postoperative cognitive dysfunction with the use of epidural versus IV PCA morphine and Colwell and Morris [7] reported no difference in complications, including confusion, with the use of IV PCA versus IM morphine postoperatively. However, Hartrick et al. [16] and Herrick et al. [18] reported a higher incidence of postoperative cognitive dysfunction with the use of morphine PCA as compared to fentanyl PCA, and Ilahi et al. [19] found a higher incidence of postoperative cognitive dysfunction with the use of continuous epidural morphine as compared to fentanyl (23% versus 8%; $p = 0.019$). Leung et al. [29] found that IV PCA was associated with a higher risk of postoperative cognitive dysfunction as compared to oral narcotics (odds ratio [OR]: 3.75; 95% CI: 1.27–11.01), as was postoperative benzodiazepine use (OR: 2.29; 95% CI: 1.21–4.36). Marcantonio et al. [33] reported similar increased risk for delirium with the use of either long- or short-acting benzodiazepines, as well as both epidural and IV meperidine.

These findings are, however, tempered by the fact that nine of the 12 studies did not report any details on how confusion and/or delirium were defined and diagnosed [7, 15, 16, 18–20, 27, 34], and no studies appeared to assess the rate of postoperative cognitive dysfunction beyond discharge from hospital.

Discussion

Surgeons and healthcare organizations continue to be pressured to increase the efficiency of care associated with

Table 4. Summary of studies comparing the effect of multimodal anesthesia protocols on POCD

Study	Year	Study group	Age (years)*	Multimodal group		Standard group		Variables evaluated	Assessment time	Findings
				Details	Number of patients	Details	Number of patients			
Retrospective comparative studies										
Hebl et al. [17]	2005	TKA, THA	67 (55–72)	Multimodal with continuous lumbar plexus catheter	40	Nonmultimodal pathway anesthesia	40	Cognitive dysfunction (method not specified)	Not specified	Cognitive dysfunction higher in nonmultimodal group (15% vs 0%; $p < 0.01$)
Peters et al. [36]	2006	TKA, THA	59 (NR)	Spinal with bupivicaine + fentanyl; preop and postop long-acting narcotic + NSAIDS; intraarticular injection: femoral nerve block + catheter in TKA	100	GA or spinal (with bupivicaine + morphine); IV PCA postop; femoral nerve block + catheter in TKA	100	Confusion (method not specified)	Not specified	Higher POCD in multimodal group (8% vs 4%; $p = 0.372$)

* Values are expressed as mean, with range in parentheses; POCD = postoperative cognitive dysfunction; NR = not reported; preop = preoperative; postop = postoperative; GA = general anesthesia; IV PCA = intravenous patient-controlled analgesia.

elective joint arthroplasty, as well as to further reduce the incidence of adverse events. While a number of advances have been made in both intra- and postoperative pain management techniques during joint arthroplasty, and while the effectiveness of various modalities on pain control and postoperative mobilization have been extensively studied, less is known about the impact on postoperative cognitive dysfunction, which remains one of the more common adverse events after TKA and THA. For this reason, we undertook the present systematic review to assess the current state of knowledge concerning the association between anesthesia and pain management strategies and postoperative cognitive dysfunction. We found that general anesthesia may be associated with early postoperative cognitive dysfunction, with no effect seen beyond 7 days. Optimization of depth of sedation through the use of adjunct monitoring may also be beneficial, although evidence is limited. While multimodal anesthesia protocols themselves were not found to reduce the incidence of postoperative cognitive dysfunction, strategies that minimized the use of narcotic medications postoperatively did appear to be helpful.

We acknowledge several limitations of the present study. First, despite using a carefully constructed, inclusive, and systematic search strategy following generally accepted methodology, it is possible that we nevertheless failed to identify one or more studies that assessed the incidence or risk of postoperative cognitive dysfunction associated with anesthetic and/or pain management techniques. This may especially be true for studies that did not have the assessment of postoperative cognitive dysfunction as a primary or secondary outcome measure but nevertheless reported it in the body of the text. Second, the reporting of results is limited by considerable heterogeneity in patient populations, methods of assessment of postoperative cognitive dysfunction, anesthetic techniques, and time points of assessment. Furthermore, a number of the included studies did not specify what criteria were used for the diagnosis of confusion and/or cognitive dysfunction. Together, these variations rendered quantitative analysis of aggregated results (as one might do in a formal meta-analysis) impossible. Nevertheless, given the considerable number of citations reviewed and the high proportion of prospective randomized studies included in the final review, we believe that our review does provide important insight into the questions posed at the study outset.

We identified several findings that will be of interest to surgeons and anesthesiologists alike. The available evidence suggests that general anesthesia is associated with increased rates of postoperative cognitive dysfunction in the early postoperative period, although no differences were identified beyond Postoperative Day 7. Unfortunately, it was not

Table 5. Summary of studies comparing the effect of different postoperative pain management regiments on postoperative cognitive dysfunction

Study	Year	Study group	Age (years)*	Anesthetic	Group 1		Group 2		Group 3	
					Intervention	Number of patients	Intervention	Number of patients	Intervention	Number of patients
Prospective randomized blinded studies										
Goyal et al. [15]	2013	TKA	64 (35–81)	Spinal	Intraarticular bupivicaine infusion × 2 days	80	Intraarticular normal saline infusion × 2 days	80		
Langford et al. [27]	2009	Noncardiac major surgery	53 (18–80)	Variable	IV parexocib × 3 days, then oral valdecoxib × 7 days; opioids as needed	525	IV placebo × 3 days, then oral placebo × 7 days; opioids as needed	525		
Marino et al. [34]	2009	THA	67 (NR)	Spinal	Continuous lumbar plexus block (ropivicaine) + PCA	75	Continuous FNB (ropivicaine) + PCA	75	PCA (hydromorphone)	75
Inan et al. [20]	2007	TKA, THA	69 (60–75)	GA	Epidural PCA (morphine)	24	IV PCA (morphine)	24		
Leung et al. [29]	2006	Noncardiac major surgery	74 (65–95)	GA	Delirium +	100	No delirium	128		
YaDeau et al. [48]	2005	TKA	73 (NR)	Spinal + PCEA (bupivicaine + hydromorphone)	Single-injection FNB	41	No FNB	39		
Prospective randomized studies										
Hartrick et al. [16]	2006	THA	63 (median; mean and range NR)	Variable	Fentanyl transdermal PCA	395	Morphine IV PCA	404		
Herrick et al. [18]	1996	TKA, THA	72 (65–85)	Variable	PCA morphine	49	PCA fentanyl	47		
Colwell and Morris [7]	1995	TKA, THA	NR	Spinal	IV PCA morphine	91	IM morphine prn	93		
Williams-Russo et al. [46]	1992	Bilateral TKA	68 (NR)	GA	Epidural bupivicaine + fentanyl infusion	25	IV fentanyl infusion	26		
Case-control studies										
Marcantonio et al. [33]	1994	Noncardiac major surgery	73 (NR)	Variable	Delirium +	91	No delirium	154		
Retrospective comparative studies										
Ilahi et al. [19]	1994	TKA	67 (33–86)	GA	Continuous fentanyl + bupivicaine epidural	80	Continuous morphine + bupivicaine epidural	56		

Table 5. continued

Study	Variables evaluated	Assessment time	Group 1 incidence	Group 2 incidence	Group 3 incidence	Findings
Prospective randomized blinded studies						
Goyal et al. [15]	Confusion (not specified)	Not specified	2.6%	1.6%		Similar rates of confusion (p = 0.302)
						Less narcotic use in experimental group POD 2 and 3
Langford et al. [27]	Confusion (patient-reported)	POD 2, 3, 4	POD 2: 1.8%	POD 2: 5%		Lower confusion on POD 2 (p = 0.006)
			POD 3: 1.6%	POD 3: 3.6%		Similar on POD 3 (p = 0.051) and 4 (p = 0.498)
			POD 4: 1.6%	POD 4: 2.2%		
Marino et al. [34]	Delirium (details not specified)	Not specified	0%	1.3%	10.70%	Higher incidence with PCA alone (p < 0.05)
Inan et al. [20]	Confusion	NR	Confusion: 12.5%	Confusion: 12.5%		No difference in rates of confusion (agitation + disorientation)
	Brief Symptom Inventory	POD 2				No difference in psychological scoring preop or postop
Leung et al. [29]	Regression analysis					Delirium associated with:
						IV PCA vs oral opioids (OR: 3.75; 95% CI 1.27–11.01)
						benzodiazepine use postop (OR: 2.29; 95% CI: 1.21–4.36)
YaDeau et al. [48]	Confusion (not specified)	Not specified	Confusion: 0%	Confusion: 2.5%		Similar incidence of confusion (p = 0.488)
						Greater volume of epidural used POD 2 in control group
Prospective randomized studies						
Hartrick et al. [16]	Confusion (not specified)	Not specified	0.3%	2.0%		Higher incidence of confusion with IV morphine (p = 0.048)
Herrick et al. [18]	Clinical confusion	Daily for 5 days	Confusion: 14%	Confusion: 4%		No difference in confusion (p = 0.160
	MMSE					Greater drop in MMSE on POD 1(p = 0.04) for morphine
	SPMSQ					Greater drop in SPMSQ on POD 5 (p < 0.05) for fentanyl
Colwell and Morris [7]	Confusion (not specified)	Not specified	NR	3% (3/93)		No difference in complications reported
Williams-Russo et al. [46]	DSM criteria for delirium	Daily				No difference in incidence of delirium
Case-control studies						
Marcantonio et al. [33]	Delirium (CAM or clinical documentation)	Daily	Meperidine: 65%	Meperidine: 42%		Higher rate with: meperidine (OR: 2.7; 95% CI: 1.3–5.5); long-acting (OR: 5.4; 95% CI: 1.0–29.2) and short-acting (OR: 2.6; 95% CI: 1.1–6.5) benzodiazepines
			Epidural: 64%	Any epidural: 42%		
			Benzodiazepine: 21%	Benzodiazepine: 8%		
Retrospective comparative studies						
Ilahi et al. [19]	Confusion (not specified)	Not specified	8%	23%		Higher incidence of confusion with epidural morphine (p = 0.019)

* Values are expressed as mean, with range in parentheses; NR = not reported; GA = general anesthesia; PCEA= patient-controlled epidural anesthesia; IV = intravenous; PCA = patient-controlled anesthesia; FNB = femoral nerve block; IM = intramuscular; MMSE = Mini Mental Status Examination; SPMSQ = Short Portable Mental Status Questionnaire; CAM = Confusion Assessment Method; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; POD = postoperative day; OR= odds ratio; preop = preoperatively; postop = postoperatively.

possible to ascertain from the available evidence whether this difference is due to the anesthetic technique per se or to a potentially modifiable factor. Nevertheless, this finding further supports the overall trend toward the use of regional techniques for elective joint arthroplasty surgery, which has found favor in part due to benefits in terms of improved postoperative pain control and decreased nausea and vomiting [32]. In patients who are operated on under general anesthesia, the optimization of depth of sedation through the use of intraoperative cerebral EEG and regional oxygenation monitoring may decrease the frequency and severity of postoperative cognitive dysfunction up to 1 year postoperatively, although this finding was limited to a single study [4]. Similarly, attention should be paid to the depth of sedation provided as an adjunct to regional anesthesia. While not specifically addressed in any of the included studies, it is possible that excessive adjunct sedation may obviate some or all of the benefits of regional techniques in terms of reducing postoperative cognitive dysfunction in the early postoperative period. There is limited evidence supporting the impact of any other variations in general or regional anesthetic techniques on postoperative cognitive dysfunction. While little has been reported on the effects of multimodal anesthetic protocols on the risk of postoperative cognitive dysfunction per se, several studies comparing different postoperative pain management strategies showed benefit for individual components typically included in multimodal protocols. This includes avoiding narcotic use through the use of single-shot or continuous peripheral nerve blocks and/or NSAIDs. Additionally, when narcotic medications are used, surgeons and anesthesiologists should preferentially select nonmorphine agents and transition to oral narcotics as soon as possible to minimize the risk of postoperative cognitive dysfunction.

While many of the anesthetic and pain management strategies identified in our review may be beneficial in terms of reducing the risk of postoperative cognitive dysfunction, it is important to recognize that the included studies may not have assessed potential risks with their use that are relevant to patients undergoing total joint arthroplasty. For example, while continuous-infusion peripheral nerve catheters may be beneficial in terms of reducing the risk of postoperative cognitive dysfunction (potentially because of decreased narcotic requirements), several authors have noted an increased incidence of complications, including muscle weakness and falls, with the use of this technique [23, 25]. Given the importance of early mobilization after total joint arthroplasty and the potentially catastrophic consequences with a fall in this context, continuous peripheral nerve blockades should be used with caution. Similarly, while the routine use of both IV and oral NSAIDs may be of benefit, the risks of major gastrointestinal complications, including fatal hemorrhage, may not be trivial in certain patient populations [5, 13]. For this reason, it is important that decisions concerning the optimal anesthetic and postoperative pain management regimens be made by surgeons, anesthesiologists, and patients together to appropriately weigh the spectrum of potential benefits and risks with different modalities.

Given the increasing use of hip and knee arthroplasty in younger populations and the resultant trend toward a wider age distribution for patients undergoing total joint arthroplasty [28, 40, 43], different anesthetic and pain management techniques may be appropriate in different patient populations based on the patient-specific risk for postoperative cognitive dysfunction. It is well documented in the general surgical population that certain patient factors such as older age and preexisting cognitive impairment increase the risk of perioperative delirium [6, 8, 9, 31], and these patients in particular may benefit from the use of anesthetic techniques that emphasize minimization of the risk of postoperative cognitive dysfunction. Additionally, other factors such as visual or hearing impairment, the use of restraints, dehydration, and administration of medications such as centrally acting antihistamines or benzodiazepines have been associated with an increased risk for delirium in a variety of hospitalized patient populations, and appropriate management of these factors should be incorporated into clinical care pathways. Nevertheless, further work is needed to better define and quantify potential risk factors for postoperative cognitive dysfunction in patients scheduled to undergo elective joint arthroplasty procedures and to assess the clinical benefit and cost-effectiveness of different anesthetic and pain management strategies based on preoperative risk stratification.

In summary, both anesthetic and pain management strategies do appear to influence the risk of cognitive dysfunction after elective joint arthroplasty. Despite the substantial number of prospective randomized studies found, the wide variety of anesthetic techniques and analgesic regimens used in the reviewed studies, as well as the variability in methodology used to diagnose postoperative cognitive dysfunction and the assessment time points, limits interpretation of the results. However, while the evidence available to date is quite heterogeneous, it does suggest that the optimal strategy includes the use of regional anesthesia, combined with multimodal techniques that minimize the need for postoperative narcotics in general, and especially avoiding the use of nonoral narcotics or morphine in any form. The authors strongly encourage other investigators to adopt the use of widely accepted, validated tools for the assessment of postoperative cognitive dysfunction. Additionally, detailed reporting of the potential risk factors and the anesthetic and analgesic techniques will facilitate future meta-analyses that can adequately control for the wide range of potential factors

affecting the risk of postoperative cognitive dysfunction and help better define optimal anesthetic and pain management strategies for elective joint arthroplasty.

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