Anesthesia Technique and Mortality after Total Hip or Knee Arthroplasty

A Retrospective, Propensity Score–matched Cohort Study

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ABSTRACT

Background: This propensity score–matched cohort study evaluates the effect of anesthetic technique on a 30-day mortality after total hip or knee arthroplasty.

Methods: All patients who had hip or knee arthroplasty between January 1, 2003, and December 31, 2014, were evaluated. The principal exposure was spinal *versus* general anesthesia. The primary outcome was 30-day mortality. Secondary outcomes were (1) perioperative myocardial infarction; (2) a composite of major adverse cardiac events that includes cardiac arrest, myocardial infarction, or newly diagnosed arrhythmia; (3) pulmonary embolism; (4) major blood loss; (5) hospital length of stay; and (6) operating room procedure time. A propensity score–matched-pair analysis was performed using a nonparsimonious logistic regression model of regional anesthetic use.

Results: We identified 10,868 patients, of whom 8,553 had spinal anesthesia and 2,315 had general anesthesia. Ninety-two percent (n = 2,135) of the patients who had general anesthesia were matched to similar patients who did not have general anesthesia. In the matched cohort, the 30-day mortality rate was 0.19% (n = 4) in the spinal anesthesia group and 0.8% (n = 17) in the general anesthesia group (risk ratio, 0.42; 95% CI, 0.21 to 0.83; $P = 0.0045$). Spinal anesthesia was also associated with a shorter hospital length of stay (5.7 *vs.* 6.6 days; $P < 0.001$).

Conclusions: The results of this observational, propensity score–matched cohort study suggest a strong association between spinal anesthesia and lower 30-day mortality, as well as a shorter hospital length of stay, after elective joint replacement surgery.

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TOTAL joint arthroplasty (TJA) is a common surgical intervention aimed at improving pain and function in patients with advanced hip or knee arthritis.[1–3] As the global population ages over time, the prevalence of adults living with severe arthritis increases significantly and so does the need for TJA.[4,5] Patients undergoing TJA in North America currently tend to be younger but have a higher comorbidity burden than those who had undergone the procedure two decades ago.[6–8] Older age, male gender, preexisting comorbidities, and the use of cemented prosthesis are well-documented risk factors for death and major morbidity after TJA.[9–11] Neuraxial anesthesia has been associated with decreased morbidity, in particular, with a reduction in blood loss[12,13] and surgical site infections[14] and a lower rate of admission to critical care services, compared to general anesthesia, for TJA.[10]

However, outcome data related to the impact of anesthetic technique on postoperative mortality after TJA are limited. With mortality rates in the range of 1 to 4 in 1,000 patients, previous clinical randomized controlled trials have been underpowered for this outcome. In addition, many studies published over 30 yr ago may no longer reflect current surgical and anesthesia practice or modern thromboprophylactic regimens.[13,15]

What We Already Know about This Topic

- The effects of spinal *versus* general anesthesia on 30-day mortality after total hip or knee arthroplasty remain unclear
- A propensity score–matched pair analysis was performed in 4,270 patients

What This Article Tells Us That Is New

- In the matched cohort, 30-day mortality rate was 0.19% (n=4) for those receiving spinal anesthesia and 0.8% (n=17) for those receiving general anesthesia (risk ratio, 0.42; 95% CI, 0.21 to 0.83; $P = 0.0045$)
- There was an association between spinal anesthesia and lower 30-day mortality

To address the issues of inadequate statistical power and limited generalizability, we performed a propensity score–matched cohort study of all patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) at the Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada, over a 12-yr period. Our primary objective was to evaluate whether spinal (intrathecal) anesthesia is associated with a reduction in 30-day mortality after elective THA or TKA compared to general anesthesia.

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Materials and Methods

Study Design

After receiving Research Ethics Board approval from the University Health Network (CAPR ID 06-0193-AE), we used the University Health Network Electronic Data Warehouse to access the clinical, laboratory, and outcome data and further cross-referenced to the Operating Room Scheduling Office System surgical database from the same institution for greater accuracy. The mortality outcome was obtained from the hospital discharge database.

Study Cohort

We retrospectively identified all patients who underwent THA or TKA at the University Health Network from January 1, 2003, to December 31, 2014. The principal exposure under investigation was spinal anesthesia *versus* general anesthesia. The primary outcome was 30-day mortality. Secondary outcomes were (1) perioperative myocardial infarction (MI); (2) a composite of major adverse cardiac events (MACE) that included cardiac arrest, MI, or newly diagnosed arrhythmia; (3) pulmonary embolism (PE); (4) major blood loss defined as greater than 2 units of packed erythrocytes during the hospital admission; (5) hospital length of stay; and (6) operating room procedure time.

Demographic data extracted included age, sex, type of surgical procedure (THA or TKA), and American Society of Anesthesiologists' (ASA) physical status classification. Baseline clinical data extracted also included a preexisting diagnosis of diabetes, cancer, metastatic cancer, anemia (as per the World Health Organization definition, less than 120 g/l for women and less than 130 g/l for men), chronic renal failure (defined as an estimated glomerular filtration rate less than 60 ml/min), chronic obstructive pulmonary disease (COPD), preexisting cardiac disease, including MI, congestive heart failure (CHF), cerebrovascular disease, peripheral vascular disease (PVD), and the revised cardiac risk index (RCRI). Baseline hemoglobin and creatinine levels were also documented.

Several processes of perioperative care have gradually and systematically changed at our institution over the past 12 yr. These changes were intended to enhance early ambulation, minimize perioperative complications, and expedite hospital discharge. Therefore, the calendar year during which each surgical procedure occurred was noted and accounted for in the analysis.

The standard surgical practice over the study period was to perform cemented TKAs and noncemented THAs. A standard general anesthetic during the study period consisted of intravenous induction with propofol with or without muscle relaxation and maintenance with inhalational agents (isoflurane, desflurane, or sevoflurane). Standard institutional practice for spinal anesthesia consisted of bupivacaine 12.5 to 15 mg with or without 100 μg of morphine, both administered intrathecally *via* a lumbar puncture, and conscious sedation with midazolam and propofol. An indwelling urinary catheter was routinely used for 24 to 48 h before 2006, but rarely used after 2006. Standard perioperative antibiotics were administered intravenously for 24 to 48 h for prophylaxis of surgical site infection. All patients in the cohort received standard perioperative thromboprophylaxis with low-molecular-weight heparins (dalteparin, 5,000 units, subcutaneoulsy, daily before 2010 and enoxaparin 40 mg, subcutaneoulsy, daily after 2010). Topical tranexamic acid (3 g) was used routinely intraoperatively after 2012, for the purpose of blood loss reduction. Unless otherwise contraindicated, a standard multimodal analgesic regimen consisted of acetaminophen 650 to 1,000 mg, orally, four times daily for 5 days, celecoxib 100 to 200 mg, orally, two times daily for 5 days, and low-dose oral opioid (1 to 2 mg of oral hydromorphone or equivalent) on an as-needed basis. In addition, patients undergoing TKA between 2003 and February 2012 received a continuous femoral perineural infusion of 0.2% ropivacaine at 5 to 10 ml/h for 48 to 72 h. After February 2012, TKA patients received an adductor canal block with 20 ml of 0.5% ropivacaine followed by intraoperative local infiltration of the joint with 300 mg of ropivacaine, 30 mg of ketorolac, and 0.6 mg of epinephrine. The standard postoperative active physiotherapy regimen was supervised by physiotherapists once daily before 2008 and twice daily starting in 2008.

Statistical Analyses

Bivariate tests were initially used to compare the characteristics of patients who had spinal anesthesia *versus* those who had general anesthesia (Mann–Whitney U test, chi-square test, and Fisher exact test). To reduce the impact of treatment-selection bias on study outcomes, we used propensity score–matched-pair analyses to determine the adjusted association of spinal anesthesia with the primary (30-day mortality) and secondary outcomes.

The rationale and methods underlying the use of propensity scores for proposed causal exposure variables in the context of cohort studies have been previously described.[16,17] We used an iterative process to develop a nonparsimonious multivariate logistic regression model to estimate a propensity score for spinal anesthesia. Perioperative variables with large standardized differences were forced into the model *a priori*. With each successive model, we checked for a balance between the two cohorts, using the standardized difference to compare the balance between groups, and imbalanced variables were likewise forced into the next model. The process continued, blinded to outcome, until all standardized difference was less than 6%. Austin[18] has postulated that the acceptable standardized difference in a matched pair is related to the sample size. Under the null hypothesis and for a sample size of 2,300 pairs, the 97th percentile of the variability in standardized differences is expected to range from −6 to 6%. Assuming we were able to match 100% of our general anesthetic patients (n = 2,135), our *a priori* goal was

to achieve a standardized difference of less than 6%. We were widely inclusive in our criteria, incorporating all variables available to us that either are known to be associated with or could conceivably be associated with increased morbidity and mortality. These variables included age, sex, year of the surgical procedure, and joint involved (either hip or knee), and all comorbidities included in the Charlson Risk Score are as follows: diabetes, preoperative anemia, chronic renal failure, cancer, metastatic cancer, COPD, asthma, obstructive sleep apnea, cardiovascular disease, cerebrovascular disease, and PVD. In addition, the ASAs' physical status classification (ASA score), the RCRI, and chronic cardiovascular medications were also included in the model. There were no cases of dementia documented in any patient in our cohort, so this was not included in the model. Similarly, only elective total joint replacements performed during regular operating room hours (Monday to Friday 8:00 AM to 5:00 PM) were studied in our cohort. So, the time of day was not included in the model. Otherwise, no potential candidate predictors were excluded.

A "greedy" matching process was used starting with five digits and performed without replacement (*i.e.*, once matched, a subject became unavailable for further matches). As a result, each final matched pair in our cohort consists of discrete individuals without repetition. The absolute standardized differences between groups were calculated after matching to ensure that the two groups were similar in all baseline characteristics. Finally, results are expressed as relative risk ratios (RRs) with a 95% CI band for dichotomous variables or proportions and median plus interquartile range for continuous variables. All *P* values were two tailed, with statistical significance defined at $P < 0.05$. Analyses were performed using SAS version 9.1 (SAS Institute Inc., USA) and R 2.4.1 (https://www.r-project.org/; accessed July 13, 2016).

Results

The study cohort consisted of 10,868 patients (5,921 knee and 4,947 hip replacements), 79% (8,553) of whom received spinal anesthesia with the remaining 21% (2,315) receiving general anesthesia. The proportion of patients who had spinal anesthesia increased progressively over the years, from 34% in 2003 to 91% in 2014. Patients who had spinal anesthesia were more likely to undergo a knee replacement compared to those who had general anesthesia. They also had a lower burden of comorbid conditions as evidenced by a lower incidence of ASA class 3 and 4 and RCRI of 3. They had a lower incidence of a preexisting diagnosis of metastatic cancer, previous MI, CHF, PVD, and anemia. They were less likely to be on chronic β-blocker therapy but more likely to be receiving calcium channel blockers or aspirin on a regular basis (table 1).

To correct for all these possible confounders, 92% (n = 2,135) of the patients who had general anesthesia were matched to similar patients who did not have general anesthesia (table 2). The covariate balance between the spinal and general anesthesia groups improved substantially through propensity score matching (table 2), with the mean standard difference after matching being 0.002 (range, −0.058 to 0.048).

Within the matched cohort, the 30-day mortality rate was 0.19% (n = 4) for those who had spinal anesthesia and 0.8% (n = 17) for those who had general anesthesia (RR, 0.42; 95% CI, 0.21 to 0.83; $P = 0.0045$; table 3). This difference corresponds to an absolute risk reduction of 0.61% and a number needed to treat of 164 patients (fig. 1). The rate of postoperative MI was similar in both groups, while there was a nonsignificant trend toward lower rates of MACE (RR, 0.81; 95% CI, 0.76 to 1.01) and PE (RR, 0.67; 95% CI, 0.41 to 1.09). Patients who had spinal anesthesia were less likely to experience major blood loss (RR, 0.62; 95% CI, 0.47 to 0.8; $P = 0.0662$) than those who had general anesthesia. Spinal anesthesia was also associated with a shorter hospital length of stay (5.7 *vs.* 6.6 days; $P < 0.001$; fig. 2) and shorter operating room procedure time (80.5 *vs.* 84.4 min; $P < 0.0001$; table 3).

Discussion

In this population-based cohort study over a 12-yr period, spinal anesthesia was associated with a lower incidence of death within 30 days of elective total joint replacement, compared to general anesthesia. The improvement corresponded to a relative risk reduction of 58% and an absolute risk reduction of 0.61%. We also found that patients receiving spinal anesthesia had a lower incidence of major blood loss, a shorter operating room procedure time, and a shorter hospital stay than those receiving general anesthesia. Given the nature of the data source, the actual causes of death cannot be ascertained. However, the greater number of documented cases of MACE, PE (albeit not statistically significant), and major blood loss in the general anesthesia group suggest plausible reasons for the difference in mortality.

This is the first study that reports a strong association between anesthetic technique and 30-day mortality after lower limb arthroplasty. Although a previous association between regional anesthesia and decreased mortality was suggested in a retrospective study by Bulka *et al.*,[19] it is uncertain whether those results are pertinent to total joint replacements given that the types of surgical procedures were undisclosed, other than the fact that they were inpatient procedures amenable to either regional or general anesthesia. In addition, most of the important patient markers of morbidity and mortality (previous cardiac or respiratory conditions, diabetes, cancer, preexisting anemia, and major-organ dysfunction) were not taken into account in their model, which significantly limits the internal and external validity of that previous study.[20]

Previous prospective studies have suggested several outcome benefits of spinal anesthesia compared to general anesthesia, but have been consistently underpowered for

Table 1. Baseline Characteristics of All Patients in the Study Period

	General Anesthesia (n = 2,315)		Regional Anesthesia (n = 8,553)		Total Cohort (n = 10,868)		
	n	%	n	%	n	%	*P* Value
Age (yr), mean (SD)	64.9 (12.4)		65.9 (11.4)		65.3 (11.1)		0.235
Female gender	927	40.04	3,469	40.56	4,396	40.45	0.654
Surgical procedure							
Hips	1,229	53.09	3,718	43.47	4,947	45.52	< 0.001
Knees	1,086	46.91	4,835	56.53	5,921	54.48	< 0.001
Year							
2003	361	15.59	189	2.21	550	5.06	< 0.001
2004	255	11.02	297	3.47	552	5.08	< 0.001
2005	281	12.14	386	4.51	667	6.14	< 0.001
2006	186	8.03	625	7.31	811	7.46	0.238
2007	257	11.1	656	7.67	913	8.4	< 0.001
2008	182	7.86	721	8.43	903	8.31	0.380
2009	218	9.42	730	8.54	948	8.72	0.182
2010	133	5.75	790	9.24	923	8.49	< 0.001
2011	83	3.59	926	10.83	1,009	9.28	< 0.001
2012	104	4.49	948	11.08	1,052	9.68	< 0.001
2013	139	6	1,136	13.28	1,275	11.73	< 0.001
2014	116	5.01	1,149	13.43	1,265	11.64	< 0.001
Comorbidities							
Diabetes	212	9.16	800	9.35	1,012	9.31	0.774
Cancer	25	1.08	69	0.81	94	0.86	0.208
Metastatic cancer	15	0.65	15	0.18	30	0.28	< 0.001
COPD	212	9.2	797	9.3	10.09	9.2	0.813
Previous MI	409	17.67	939	10.98	332	3.05	< 0.001
CHF	60	2.59	138	1.61	198	1.82	0.002
CVD	64	2.76	198	2.31	262	2.41	0.211
PVD	27	1.17	61	0.71	88	0.81	0.031
CRF	45	1.94	132	1.54	177	1.63	0.177
Anemia	409	17.67	939	10.98	1,348	12.4	< 0.001
Chronic CV medications							
β-blockers	494	21.34	1,547	18.09	2,041	18.78	< 0.001
ACE inhibitors	500	21.6	1,821	21.29	2,321	21.36	0.749
Calcium channel blockers	371	16.03	1,545	18.06	1,916	17.63	0.022
Aspirin	339	14.64	1,554	18.17	1,893	17.42	< 0.001
Statin	620	26.78	2,188	25.58	2,808	25.84	0.242
ASA class							
I	65	2.81	239	2.79	304	2.8	0.972
II	1,078	46.57	4,486	52.45	5,564	51.2	< 0.001
III	1,085	46.87	3,684	43.07	4,769	43.88	< 0.001
IV	87	3.76	144	1.68	231	2.13	< 0.001
RCRI							
0	1,842	79.57	6,848	62.96	8,684	79.9	0.596
1	368	15.9	1,392	12.81	1,760	16.19	0.661
2	87	3.76	289	2.66	376	3.46	0.376
3	18	0.78	30	0.28	48	0.44	0.006
Total	2,315		8,553		10,868	100	

ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CV = cardiovascular; CVD = cerebrovascular disease; MI = myocardial infarction; PVD = peripheral vascular disease; RCRI = revised cardiac risk index.

mortality, a relatively rare outcome in this elective surgical population. A recent systematic review of the literature[15] identified only two randomized controlled trials (RCTs) reporting mortality rates after THA, but with sample sizes of 88 and 188, respectively, they lacked the statistical power to find a potential difference.[20,21] Similarly, another systematic review of THA and TKA identified only two RCTs, both of which were underpowered for mortality,[22] while a

Table 2. Baseline Patient Characteristics in the Propensity Score–matched Cohorts

	General Anesthesia (n = 2,135)		Spinal Anesthesia (n =2,135)		Absolute Standardized Difference (after Matching)
	n	%	n	%	
Age (yr), median (IQR)	65.8 (65.3–66.4)		65.7 (65.2–66.2)		0.008
Female gender	842	39.44	859	40.24	–0.058
Surgical procedure					
Hips	1,109	51.94	1,103	51.66	0.005
Knees	1,026	48.06	1,032	48.34	–0.004
Year					
2003	217	10.16	181	8.48	0.043
2004	233	10.92	251	11.76	–0.017
2005	273	12.78	271	12.70	0.001
2006	185	8.66	203	9.5	–0.024
2007	254	11.9	300	14.06	–0.041
2008	182	8.52	177	8.30	0.005
2009	216	10.12	217	10.16	0.001
2010	133	6.22	135	6.32	–0.006
2011	83	3.76	57	2.66	0.048
2012	104	4.88	106	4.96	–0.006
2013	139	6.52	130	6.08	0.017
2014	116	5.44	107	5.02	0.013
Comorbidities					
Diabetes	65	6	61	5.8	0.006
Cancer	24	1.12	18	0.84	0.028
COPD	193	18.6	195	18.8	0.002
Previous MI	84	3.94	64	3	0.038
CHF	56	2.62	50	2.34	–0.033
CVD	62	2.90	53	2.48	0.017
PVD	25	1.18	21	0.98	0.014
CRF	43	2.02	39	1.82	0.010
Anemia	350	16.4	324	15.18	0.022
Baseline hemoglobin (g/L)	134.6 (133–135)		135.4 (124.5–136.1)		0.005
Baseline serum creatinine (μm/L)	81.8 (79.8–83.8)		81.3 (79.4–83.8)		0.043
Chronic CV meds					
β-blockers	453	21.2	453	21.2	0.000
ACE inhibitors	459	21.5	518	12.1	–0.041
Calcium channel blockers	346	16.2	406	19.0	–0.049
Aspirin	314	30.2	335	16.0	–0.028
Statin	585	27.4	588	27.5	–0.003
ASA classification					
I	59	2.8	52	2.4	0.009
II	987	46.2	958	44.8	0.017
III	1,015	47.5	1,059	49.6	–0.023
IV	74	3.5	66	3.1	0.008
RCRI					
0	1,692	78.7	1,694	79.3	0.001
1	346	16.2	346	16.2	–0.014
2	81	3.8	88	4.1	0.037
3	16	0.7	7	0.3	0.014

ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CV = cardiovascular; CVD = cerebrovascular disease; IQR = interquartile range; MI = myocardial infarction; PVD = peripheral vascular disease; RCRI = revised cardiac risk index.

previous meta-analysis of anesthetic technique for THA did not report mortality outcomes.[13] A population-based retrospective study on 7,977 patients who had TJA in Taiwan between 1997 and 2010 reported a small advantage (58 *vs.* 57%) in long-term survival (over 14 yr) for neuraxial compared to general anesthesia.[23] Our findings are consistent with those of three systematic reviews comprising most of the evidence from the 1970s to the early 2000s, suggesting that spinal anesthesia results in lower rates of thromboembolic events and major blood loss and/or lower transfusion

Table 3. Results

	General Anesthesia (n = 2,135)		Spinal Anesthesia (n = 2,135)			
	n	%	n	%	RR (95% CI)	*P* Value
Dichotomous outcomes						
Death	17	0.8	4	0.19	0.42 (0.21–0.83)	0.0045
MI	28	1.31	27	1.27	0.97 (0.61–1.7)	0.892
MACE	36	1.69	29	1.36	0.81 (0.76–1.01)	0.3816
PE	25	1.17	18	0.84	0.67 (0.41–1.09)	0.2832
Blood transfusion > 2 units	93	4.36	70	3.28	0.62 (0.47–0.8)	0.0662
	Median	IQR	Median	IQR		*P* Value
Continuous outcomes						
Length of stay (days)	6.61	6.2–7.0	5.7	5.3–6.1		0.0001
OR time (min)	84.4	(83–85.8)	80.5	(79.7–81.7)		0.0001

IQR = interquartile range; MACE = major adverse cardiac events; MI = myocardial infarction; OR = operating room; PE = pulmonary embolism; RR = risk ratio.

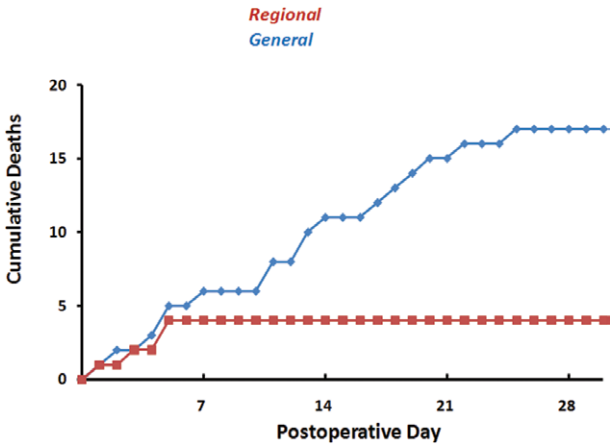

Fig. 1. Cumulative number of deaths over time within 30 days of the surgical procedure.

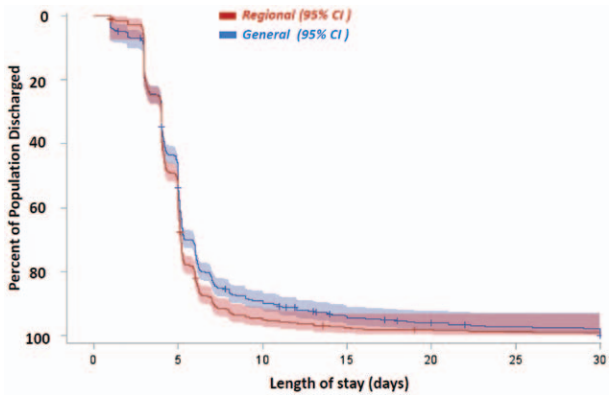

Fig. 2. Percentage of the population discharged from hospital over time.

requirements.[13,15,22] The trend we observed toward a lower rate of PE was somewhat surprising, given that all patients in this study received potent thromboprophylaxis with low–molecular weight heparin. Given the low baseline incidence of PE in our patient population (1.17%), an even larger sample size would be required for statistical significance.

Several observational studies using data from administrative databases have reported that male gender, older age, a preexisting history of CHF, bilateral surgery, and the use of a cemented prosthesis are all risk factors for mortality after major joint replacement. However, anesthetic technique is often not captured in administrative databases and therefore not reported in these large studies.[9,11,24–26]

A population-based study of 15,000 patients undergoing bilateral TKA from 2006 to 2010 reported similar mortality rates between those receiving neuraxial and those receiving general anesthesia (0.1%).[12] There are several differences between our study and that by Stundner *et al.*[12] First, patients in our cohort tended to be older, have a higher comorbidity burden, and include a greater proportion of men, all of which are associated with mortality, thus making our cohort potentially more susceptible to the effects (both negative and positive) of the anesthetic techniques.[9,11,24–26] In addition, the two groups in Studner's study were unbalanced, with 95% of patients receiving general anesthesia. The small proportion of patients who received neuraxial block (about 5% of the total sample) could limit the ability to find a mortality difference in that setting.

Our study has several strengths. First, our relatively large sample size allowed us to detect small treatment effects that would have been deemed nonsignificant in smaller studies. Second, the propensity score matching allowed us to minimize baseline differences between the groups, thus limiting the extent of treatment selection bias inherent of a retrospective study. Taking into account the year of the surgical procedure into the propensity score minimized the potential confounding due to the unmeasured effects of changes in processes of care that took place during the 12-yr period. Finally, this clinical database offered significant granularity in terms of demographic information and preexisting cardiovascular comorbidities, which are important independent risk factors for morbidity and mortality. Conversely,

our study has several limitations. First, the causes of death were not documented on our data sources. Such information could have helped to better describe how spinal anesthesia improves mortality. A second limitation stems from the limited data on noncardiac comorbidities, such as underlying COPD, obstructive sleep apnea, pulmonary hypertension, and postoperative respiratory complications. In addition, the fact that this is a single-center study limits the generalizability of the conclusions to other centers with differing practices.

An important question that needs to be considered is whether the results of this study are evidence of causality or a mere association between spinal anesthesia and lower mortality after TJA. The traditional framework of proof of causality is based on a number of criteria commonly attributed to Hill[27] and include (1) temporal relationship between the exposure and the outcome, (2) strength of the association, (3) the existence of a dose–response effect, (4) consistency of the findings, (5) plausibility, (6) specificity, (7) coherence, (8) alteration by experiment, and (9) the consideration of alternate explanations.[27] These criteria developed in the mid-1960s just as the realization of the potent effect of smoking on lung cancer was taking hold and drove much of healthcare research over the next 50 yr. The premise that spinal anesthesia may have a positive impact on mortality after total joint replacement indeed meets several of Hill criteria. In particular, there is an appropriate temporal relationship (*i.e.*, the anesthetic intervention precedes the outcome of death); it is plausible given the different systemic effects of spinal and general anesthesia on major organ systems, and the findings are coherent and consistent with previous data that show decreased morbidity with both spinal and epidural anesthesia in a variety of surgical settings.[28–31] Within this traditional framework, the ultimate gold standard experimental design to infer causality is an RCT. Nevertheless, RCTs are often not feasible to study relatively rare outcomes (such as the case of mortality after total joint replacement).[32] The large sample size needed to demonstrate a significant difference prospectively would require an unusually lengthy and costly process, which is unlikely to be feasible or fundable.[33] In fact, all previous RCTs of patient outcomes after total joint replacements in the past four decades were grossly underpowered for mortality (sample sizes between 20 and 210), and most of them did not even report this outcome.[13,15,22] A larger multicenter study (the Multicenter Australian Study of Epidural Anesthesia and Analgesia in Major Surgery trial) that investigated the effect of epidural anesthesia and analgesia on major outcomes in an unselected surgical population took 7 yr to complete, and it was nonetheless underpowered for mortality.[34] Due to these limitations, there is a growing realization that much of our knowledge of causal effects in current health care must come from nonrandomized observational studies, especially when evaluating relatively rare but clinically important outcomes.[32] While the utility of long-used familiar approaches for statistical analysis and causal inferences is diminishing, more modern causal inference studies on population-based data are particularly useful and are often directed not at identifying causes, but at identifying effects of interventions.[32] In order for observational data to be accurately interpreted, the studies need to be designed in such a way that they emulate hypothetical randomized experiments with relatively well-defined interventions and measures aimed at minimizing confounding factors.[16,17,35,36] Propensity score methods, such as the one used in the current study, are examples of such designs, as they objectively create subgroups that are balanced with respect to all observed relevant covariates.[16,17,35,36] The main advantage of RCTs over observational studies is that the process of randomization creates groups that are equal in all aspects except for the intervention or exposure of interest, eliminating the potential effect not only of known confounders, but also of unknown or unmeasured confounders. Therefore, although the strength of the evidence from the current observational study is lower than that of an RCT, it is compelling as probably the best quality of evidence that is available to date on the relationship between anesthesia technique and mortality after major joint arthroplasty.

Conclusion

The results of this observational, propensity score–matched cohort study suggest a strong association between spinal anesthesia and lower 30-day mortality, as well as a shorter hospital length of stay, after elective total joint replacement surgery.

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Competing Interests

Dr. Chan has received honoraria from SonoSite (Bothell, Washington) and Abbvie (Quebec, Canada) and is a member of the Medical Advisory Board for Smiths Medical (St. Paul, Minnesota) and Philips Healthcare (Markham, Ontario, Canada). The other authors declare no competing interests.

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