DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Monday May 1, 2017
1800 HOURS

LOCATION:
Mino's Downtown-340 Barrie Street

PRESENTING ARTICLES:
Dr. Joanna Dion & Dr. Jeff Parker

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

Postoperative Medical Complications Associated with Anesthesia in Older Adults with Dementia

Dallas P. Seitz, MD,[a] Sudeep S. Gill, MD, MSc,[b,c] Chaim M. Bell, MD, PhD,[c,d,e] Peter C. Austin, PhD,[c,d] Andrea Gruneir, PhD,[c,d,f] Geoff M. Anderson, MD, PhD,[c,d] and Paula A. Rochon, MD, MPH[c,d,f]

OBJECTIVES: To examine the association between anesthetic technique and postoperative complications in older adults with dementia undergoing hip fracture surgery.

DESIGN: Population-based, retrospective cohort study.

SETTING: Ontario, Canada.

PARTICIPANTS: All older adults with dementia who underwent surgery for hip fracture repair in Ontario, Canada, between April 1, 2003 and March 31, 2011.

MEASUREMENTS: The baseline characteristics of individuals who received general anesthesia (GA) and regional anesthesia (RA) were compared. Individuals who received GA were matched to similar individuals who received RA using propensity scores to control for confounding, and their outcomes compared, including 30-day mortality, intensive care unit (ICU) admissions, specific postoperative medical complications, and hospital length of stay (LOS).

RESULTS: In the 6,135 matched pairs, there was no statistically significant difference in postoperative 30-day mortality (GA, 11.3%; RA, 10.8%, $P = .44$). There were no statistically significant differences in the rates of specific postoperative medical complications or LOS in the two anesthetic groups, but GA was associated with higher rates of ICU admissions (6.1% vs 4.2%, $P < .001$).

CONCLUSION: For older adults with dementia undergoing hip fracture surgery, GA and RA are associated with similar rates of most perioperative adverse events. Further studies are required to determine the optimal methods of providing anesthesia and perioperative care for older adults with dementia undergoing surgical procedures. **J Am Geriatr Soc 62:2102–2109, 2014.**

From the Departments of [a]Psychiatry, [b]Medicine, Queen's University, Kingston; [c]Institute for Clinical Evaluative Sciences, Toronto; [d]Institute of Health Policy, Management and Evaluation, University of Toronto; [e]Department of Medicine, Mt. Sinai Hospital; and [f]Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada.

Address correspondence to Dr. Dallas Seitz, Department of Psychiatry, Queen's University, Providence Care Mental Health Services, Kingston, Ontario K7L 4X3, Canada. E-mail: seitzd@providencecare.ca

DOI: 10.1111/jgs.13106

Key words: hip fracture; anesthesia; surgery; Alzheimer's disease; dementia

Given the growing numbers of older adults with dementia,[1] there will be increasing numbers who will undergo surgical procedures and require postoperative care in the future.[2,3] Older adults with dementia are particularly likely to undergo certain surgical procedures such as hip fracture repair[4] because of their likelihood of having osteoporosis[5,6] and of falling.[7,8] An estimated 20% to 30% of all older adults with hip fractures have premorbid dementia,[4] and individuals with dementia are at high risk of postoperative medical complications, including mortality,[9,10] long-term care (LTC) placement,[9] and postoperative cognitive adverse events such as delirium.[11–14] Dementia has also been associated with greater risk of perioperative medical complications such as pneumonia and other infections, acute renal failure, and stroke.[15,16]

One potentially modifiable care process that may be associated with postoperative complications in older adults with dementia undergoing hip fracture repair is the type of anesthesia used during surgery. For many surgeries, anesthesia can be general (GA) or regional (RA). The selection of anesthesia is often modifiable and determined by the anesthesiologist's preference, taking into consideration pertinent medical factors and patient preference.[17] Some observational studies[18] and meta-analyses of randomized controlled trials have suggested that perioperative morbidity and mortality may be greater with GA than RA.[17,19,20] Particular postoperative complications that may be higher with use of GA include pneumonia[19] and thromboembolic events.[19] Anesthesia-related medical complications may be more common in older adults with dementia given that dementia is a risk factor for adverse perioperative events including pneumonia.[15,21] Because many individuals with dementia have impaired mobility even before hip fracture,[22] this group may also be at greater risk of thromboembolism associated with anesthesia, but prior studies on anesthesia-related adverse events have excluded individuals with dementia or included individuals with and

0002-8614/14/$15.00

without dementia in their study population. Little is known about the role that anesthetic technique may play in the postoperative medical outcomes of older adults with dementia. The current study examined the association between anesthetic technique and postoperative outcomes in older adults with dementia who underwent surgical repair of hip fractures.

METHODS

Data Sources

Several linked administrative databases available at the Institute for Clinical Evaluative Sciences (ICES) were used for this retrospective cohort study. Demographic information and date of death were identified using the Registered Persons Database. Outpatient and inpatient physician visits were identified using physician claims documented in the Ontario Health Insurance Program Database claims database. In Ontario, adults aged 65 and older are eligible for prescription drug coverage, and information on prescribed medications is contained in the Ontario Drug Benefits claims database. Inpatient hospitalizations in Ontario are captured in the Canadian Institutes for Health Information (CIHI) Discharge Abstract Database (DAD), and emergency department (ED) visits are recorded in the CIHI National Ambulatory Care Reporting System database. These databases are routinely used for research purposes, and the accuracy of the data sources has been previously described.[23,24] These data sets were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

Study Sample

All individuals admitted to any Ontario hospital between April 1, 2003, and March 31, 2011, who had experienced a hip fracture and underwent a surgical procedure to repair their hip fracture were included. Cohort entry was defined as the date of hip fracture repair. Individuals with evidence of a hip fracture associated with major trauma or elective hip surgery and those receiving palliative care or with pathological fractures were excluded. The study sample was further restricted to individuals with evidence of physician-diagnosed dementia in the 5 years preceding surgery using claims for outpatient physician visits and hospitalizations[25,26] (Data S1).

Exposure Definition

The primary exposure for the study was the type of anesthesia used for hip fracture surgery. The type of anesthesia administered for procedures is recorded in the CIHI-DAD for all inpatient surgical procedures. The primary type of anesthesia used for surgical procedures is recorded as GA or RA.[27] GA included any type of GA (including inhalational or intravenous GA) or GA combined with regional techniques such as epidural anesthesia or local anesthesia. RA was restricted to spinal anesthesia. The accuracy of the CIHI-DAD for coding of anesthetic type has been previously described and is of high quality.[27]

Baseline Characteristics and Covariates

We determined whether individuals were residing in LTC before hip fracture using LTC indicators on prescribed medications. Medical comorbidity was described using the Charlson Comorbidity Index using information from hospitalizations in the 5 years before cohort entry.[28,29] Individuals without a hospitalization in the past 5 years were categorized as "no hospitalization" for their Charlson score, and participants with at least one hospitalization were assigned a Charlson score of 0, 1, 2, or 3 or greater. The Adjusted Clinical Groups system was used to determine the number of major Adjusted Diagnostic Groups for each individual using outpatient visits and hospitalizations in the 2 years before cohort entry.[30] The number of unique medications used in the year preceding the index hospitalization was determined as another predictor of morbidity and mortality.[31] Common medical conditions that may be associated with postoperative morbidity and mortality were identified, along with markers of dementia severity (e.g., use of antipsychotic medications, urinary incontinence). Variables that might lead to preferential selection of GA over RA because of potential contraindications to RA were also ascertained. These included medical conditions (e.g., aortic stenosis), medications associated with increased risk of bleeding (e.g., warfarin or oral antiplatelet agents), and medical conditions associated with receipt of anticoagulation medications (e.g., atrial fibrillation). Perioperative variables including type of fracture, type of surgery performed, delay in timing of surgery, and characteristics of the hospitals and surgeons performing surgery were also determined. Severity of medical illness at the time of surgery was determined using anesthesiologist billing claims, which included the American Society of Anesthesiologists score at the time of surgery.[32]

Outcomes

The primary outcome was 30-day mortality, which was selected because it has commonly been used in randomized controlled trials[17,33] and observational studies evaluating anesthetic technique and hip fracture outcomes.[15,34] Postoperative medical complications that may be associated with anesthesia were also identified, including myocardial infarction, congestive heart failure, pneumonia, and thromboembolic events, including pulmonary embolism and deep vein thrombosis.[17] A composite outcome of any major postoperative complication was defined as the occurrence of any of these individual complications within 30 days after surgery. In-hospital complications that occurred during the index admission and those that required a hospital readmission or ED visit within 30 days of surgery were included. Transfers to intensive care units (ICUs) in the 7 days after surgery were reported, using a previously described approach.[25,35] Finally, length of stay for the index hospitalization was determined for all individuals.

Analysis

Baseline characteristics of individuals who received GA and RA were compared using the Wilcoxon rank-sum test for continuous variables and the chi-square test for

categorical variables. To account for systematic differences in observed baseline confounders between individuals receiving GA and those receiving RA, propensity-score matching was used to estimate the effect of anesthesia type on outcomes. A logistic regression model was used to estimate the probability of receiving GA (vs RA) using a priori–selected baseline covariates. Variables were selected based upon their potential to be predictive of the outcome.[36] The propensity score included the variables age, sex, residence before fracture (community vs LTC), Charlson Comorbidity Index score, number of major Adjusted Diagnostic Groups, number of outpatient visits in the year preceding hip fracture, angina pectoris, atrial fibrillation, congestive heart failure, chronic renal disease, diabetes mellitus, any malignancy, metastatic cancer, history of pneumonia, myocardial infarction, chronic obstructive pulmonary disease, cholinesterase inhibitor use, antipsychotic use, American Society of Anesthesiologists score, length of time between initial hospitalization and date of surgery, type of surgical repair, type of fracture, hospital type (rural, urban nonteaching, teaching), and community type (rural vs urban). Subjects who received GA were then matched to subjects who received RA on the logit of the propensity score, using calipers of width equal to 0.2 standard deviations of the logit of propensity score, creating matched pairs.[36–38] In addition to matching on propensity score, subjects were matched on age (within 1 year), sex, place of residence (LTC vs community), Charlson score, and type of hospital to facilitate subsequent subgroup analyses based on these same characteristics. The balance of baseline variables in the two exposure groups were assessed using standardized differences, with a 10% difference indicating potentially meaningful imbalance.[39]

Within the matched sample, the outcomes associated with GA were then compared with those associated with RA using the paired *t*-test for continuous outcomes and the McNemar test for binary outcomes to account for the matched nature of the samples.[37,40] To explore potential subgroups at greater risk of postoperative adverse events associated with anesthetic technique, subgroup analyses based on age, sex, residence before hip fracture, and Charlson score were performed. For all analyses, two-sided *P*-values of .05 were used as the threshold for statistical significance. SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used for all statistical analyses.

Ethics

The research ethics board at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, approved this study.

RESULTS

Description of Study Sample

During the study period, 20,973 older adults with dementia underwent hip fracture surgery in Ontario. Regional anesthesia was used for 12,155 (57.9%) hip fracture surgeries (Table 1). In the unmatched sample, older adults with hip fractures and dementia who received GA tended to be slightly younger (84.8 vs 85.3, $P < .001$), and were more likely to have resided in LTC facilities before surgery. Individuals with GA had had slightly more outpatient and ED visits in the year before hip fracture. Most measures of medical comorbidity were similar for individuals who received GA and RA, and the majority of perioperative variables were also similar.

Six thousand one hundred thirty-five individuals who received GA were matched to 6,135 individuals who received RA (69.5% of individuals who received GA successfully matched to a similar individual who received RA). After matching, most systematic differences in measured covariates between treatment groups had been substantially reduced, with antiplatelet medications being the only covariate with a standardized difference of greater than 10% (Table 1).

Outcomes Associated with GA and RA

There were high rates of morbidity and mortality observed in the entire study sample (Table 2). In the matched sample, differences in 30-day mortality (GA, 11.3%; RA, 10.8%, $P = .44$), any major postoperative complication (GA, 19.0%; RA, 19.1%, $P = .52$), and frequency of specific major postoperative complications were not statistically significant, although admissions to ICUs in the 7 days after admission were higher for individuals who received GA (6.1%) than those who received RA (4.2%) ($P < .001$). Hospital length of stay associated with receipt of GA (16.1 days) or RA (16.0 days) was similar ($P = .72$).

Subgroup Analyses

The results for the subgroup analyses based on age, sex, place of residence before admission (community-dwelling vs LTC residence), and Charlson comorbidity scores are summarized in Table 3. There were no other statistically significant differences in mortality or the composite measures of major postoperative complications between GA and RA. In some subgroups, GA was associated with a higher rate of ICU admission than RA.

DISCUSSION

In older adults with dementia who sustained hip fractures, GA and RA were associated with similar rates of postoperative mortality, specific medical complications, and hospital LOS, suggesting that anesthesia technique does not play a clinically important role in the early postoperative outcomes of this population. A slightly greater risk of ICU admission was observed for individuals who received GA, although this difference in risk of ICU admission did not translate to greater risk of other potential adverse outcomes. This population-based study of older adults with hip fracture and dementia also highlights the clinical complexity of this vulnerable group, with high rates of postoperative morbidity and mortality observed. Overall, optimization of anesthetic and perioperative management and postoperative care for individuals with dementia undergoing surgical procedures is required to improve upon current postoperative outcomes. The role of anesthesia in postoperative outcomes may be of less importance than other perioperative factors.

Table 1. Characteristics of Older Adults with Dementia who Received General or Regional Anesthesia for Hip Fracture Surgery

Characteristic	Unmatched Cohort			Matched Cohort[a]		
	General Anesthesia, n = 8,818	Regional Anesthesia, n = 12,155	Standardized Difference	General Anesthesia, n = 6,135	Regional Anesthesia, n = 6,135	Standardized Difference
Demographic characteristics						
Age, mean (± SD)	84.8 (6.6)	85.2 (6.5)	0.07	85.3 (5.7)	85.3 (5.9)	0.00
Female, n (%)	6,613 (75.0)	9,055 (74.5)	0.15	4,959 (80.8)	4,959 (80.8)	0.00
Long-term care resident, n (%)	4,091 (46.4)	5,842 (48.1)	0.03	2,854 (46.5)	2,854 (46.5)	0.00
Rural community, n (%)	635 (7.2)	1,072 (8.8)	0.04	429 (7.0)	433 (7.1)	0.00
Medical comorbidity, mean (± SD)						
Number of outpatient visits	59.1 (44.4)	56.8 (40.6)	0.05	55.2 (39.4)	56.0 (39.5)	0.02
Number of emergency department visits	1.4 (2.0)	1.4 (1.8)	0.03	1.3 (1.9)	1.3 (1.7)	0.01
Number of hospitalizations	0.46 (0.87)	0.45 (0.89)	0.01	0.40 (0.81)	0.39 (0.83)	0.01
Number of drugs	11.1 (6.2)	11.2 (6.1)	0.02	10.9 (6.0)	10.8 (5.9)	0.02
Number of major Adjusted Diagnostic Groups	2.7 (1.4)	2.6 (1.4)	0.06	2.6 (1.4)	2.6 (1.4)	0.00
Charlson score, n (%)						
No hospitalizations	3,166 (35.9)	4,385 (36.1)	0.05	2,490 (40.6)	2,490 (40.6)	0.00
0	2,713 (30.8)	3,594 (29.6)	0.08	2,019 (32.2)	2,019 (32.2)	0.00
1	1,308 (14.8)	1,775 (14.6)	0.04	779 (12.7)	779 (12.7)	0.00
2	644 (7.3)	946 (7.8)	0.00	309 (5.0)	309 (5.0)	0.00
≥3	987 (11.2)	1,455 (12.0)	0.00	538 (8.8)	538 (8.8)	0.00
Medical conditions, n (%)						
Angina pectoris	1,976 (22.4)	2,535 (20.9)	0.08	1,208 (9.7)	1,191 (19.4)	0.00
Aortic stenosis	83 (0.9)	83 (0.7)	0.04	19 (0.3)	21 (0.3)	0.00
Atrial fibrillation	1,033 (11.7)	1,410 (11.6)	0.03	631 (10.3)	616 (10.0)	0.00
Aortic valve replacement	31 (0.3)	24 (0.2)	0.03	15 (0.2)	6 (0.1)	0.04
Mitral valve replacement	≤5 (<0.1)	10 (0.1)	0.00	≤ 5 (<0.1)	≤5 (<0.1)	0.00
Congestive heart failure	2,016 (22.9)	2,893 (23.8)	0.02	1,287 (20.5)	1,268 (20.7)	0.00
Chronic obstructive lung disease	2,545 (28.9)	3,847 (31.6)	0.01	1,722 (28.1)	1,682 (27.4)	0.01
Chronic kidney disease	974 (11.0)	1,465 (12.0)	0.00	606 (9.9)	639 (10.4)	0.02
Diabetes mellitus	2,237 (25.4)	3,035 (25.0)	0.05	1,418 (23.1)	1,448 (23.7)	0.02
Deep vein thrombosis	72 (0.8)	91 (0.7)	0.01	44 (0.7)	38 (0.6)	0.01
Hypertension	6,651 (75.4)	9,185 (75.6)	0.00	4,619 (75.3)	4,647 (75.7)	0.01
Urinary incontinence	459 (5.2)	595 (4.9)	0.03	337 (5.5)	302 (4.9)	0.03
Low back surgery	19 (0.22)	8 (0.07)	0.04	7 (0.11)	≤ 5 (0.1)	0.01
Malignancy	344 (3.9)	535 (4.4)	0.01	185 (3.0)	183 (3.0)	0.00
Metastatic cancer	51 (0.6)	69 (0.6)	0.00	34 (0.5)	35 (0.6)	0.00
Parkinson's disease	418 (4.7)	638 (5.2)	0.00	284 (4.6)	295 (4.8)	0.00
Pneumonia	2,149 (24.4)	3,193 (26.3)	0.00	1,376 (22.4)	1,371 (22.3)	0.00
Myocardial infarction	3,063 (34.7)	4,068 (33.5)	0.08	1,956 (31.9)	1,924 (31.4)	0.01
Pulmonary embolism	134 (1.5)	166 (1.4)	0.02	73 (1.19)	78 (1.27)	0.00
Stroke	2,199 (24.94)	2,680 (22.0)	0.11	1,296 (20.7)	1,257 (20.5)	0.02
Medications, n (%)						
Antiplatelet	1,456 (16.5)	1,260 (10.4)	0.21	999 (16.3)	593 (9.7)	0.19
Heparin	36 (0.4)	58 (0.5)	0.00	26 (0.4)	25 (0.4)	0.00
Cholinesterase inhibitor	3,061 (34.7)	4,402 (36.2)	0.02	2,286 (37.3)	2,277 (37.1)	0.00
Antidepressant	4,052 (45.9)	5,738 (47.2)	0.05	2,841 (46.3)	2,847 (46.4)	0.00
Antipsychotic	2,787 (31.6)	3,870 (31.8)	0.05	1,987 (32.4)	1,924 (31.4)	0.02
Benzodiazepine	2,281 (25.9)	3,231 (26.6)	0.03	1,614 (26.3)	1,599 (26.1)	0.00
Warfarin	1,038 (11.8)	1,270 (10.4)	0.07	673 (11.0)	592 (9.6)	0.04
Perioperative variables						
ASA score, n (%)						
No score	2,256 (25.6)	3,113 (25.6)	0.04	2,320 (37.8)	2,322 (37.8)	0.07
3	2,937 (33.3)	3,892 (32.0)	0.08	2,048 (33.4)	2,049 (33.4)	0.00
4	2,558 (29.0)	3,727 (30.7)	0.01	1,741 (28.4)	1,740 (28.4)	0.00
5	56 (0.6)	70 (0.6)	0.01	32 (0.5)	28 (0.5)	0.00
Surgical delay, days, mean (± SD)	1.68 (5.0)	1.58 (4.3)	0.02	1.52 (2.7)	1.48 (2.5)	0.02
Hemiarthroplasty, n (%)	3,434 (38.9)	4,885 (40.2)	0.04	2,377 (50.3)	2,455 (40.0)	0.00
Intracapsular fracture, n (%)	4,437 (50.3)	6,220 (51.2)	0.06	3,084 (50.3)	3,110 (50.7)	0.08
Quartile of hospital volume for hip fracture surgery, n (%)						
1	291 (3.3)	660 (5.4)	0.09	212 (3.5)	298 (4.9)	0.07

(Continued)

Table 1. (Contd.)

Characteristic	Unmatched Cohort			Matched Cohort[a]		
	General Anesthesia, n = 8,818	Regional Anesthesia, n = 12,155	Standardized Difference	General Anesthesia, n = 6,135	Regional Anesthesia, n = 6,135	Standardized Difference
2	1,218 (13.8)	2,371 (19.5)	0.12	923 (15.0)	1,169 (19.0)	0.10
3	2,558 (29.0)	3,145 (25.9)	0.11	1,815 (29.6)	1,670 (27.2)	0.05
4	4,751 (53.9)	5,979 (49.2)	0.18	3,185 (51.9)	2,998 (48.9)	0.06
Hospital type, n (%)						
Rural	48 (0.5)	180 (1.5)	0.08	≤ 5 (<0.1)	≤ 5 (<0.1)	0.00
Urban nonteaching	6,517 (73.9)	9,500 (78.2)	0.04	5,029 (82.0)	5,029 (81.3)	0.00
Teaching	2,253 (25.5)	2,475 (20.4)	0.17	1,103 (18.0)	1,103 (18.0)	0.00
Quartile of orthopedic surgeon volume for hip fracture, n (%)						
1	567 (6.4)	618 (5.1)	0.08	349 (5.7)	288 (4.7)	0.04
2	1,113 (12.6)	1,435 (11.8)	0.05	749 (12.2)	696 (11.3)	0.02
3	1,871 (21.2)	2,604 (21.4)	0.03	1,344 (21.9)	1,319 (21.5)	0.00
4	4,204 (47.7)	6,096 (50.1)	0.02	2,996 (48.8)	3,118 (50.8)	0.04

[a] Samples were matched on propensity score, which included age, sex, residence before fracture (community vs long-term care), Charlson Comorbidity Index, number of major Adjusted Diagnostic Groups, number of outpatient visits in year preceding hip fracture, angina pectoris, atrial fibrillation, congestive heart failure, chronic renal disease, diabetes mellitus, any malignancy, metastatic cancer, history of pneumonia, myocardial infarction, chronic obstructive pulmonary disease, cholinesterase inhibitor use, antipsychotic use, American Society of Anesthesiologists (ASA) score, length of time between hospitalization and surgery, type of surgical repair, type of fracture, hospital type (rural, urban nonteaching, teaching), community type (rural vs urban).
SD = standard deviation.

Table 2. Outcomes Associated with General or Regional Anesthesia for Older Adults with Dementia Undergoing Hip Fracture Surgery

Outcome	Unmatched Cohort			Matched Cohort[a]		
	General Anesthesia, n = 8,818	Regional Anesthesia, n = 12,155	*P*-Value	General Anesthesia, n = 6,135	Regional Anesthesia, n = 6,135	*P*-Value
30-day mortality, n (%)	1,044 (11.8)	1,450 (11.9)	.84	691 (11.3)	665 (10.8)	.44
Intensive care unit admission, n (%)	616 (6.99)	584 (4.8)	<.001	371 (6.0)	259 (4.2)	<.001
Complications within 30 days, n (%)						
Any serious complication	1,827 (20.7)	2,505 (20.6)	.85	1,165 (19.0)	1,169 (19.0)	.92
Myocardial infarction	743 (8.4)	982 (8.1)	.37	501 (8.2)	454 (7.4)	.11
Congestive heart failure	788 (8.9)	1,172 (9.6)	.08	495 (8.1)	550 (9.0)	.07
Deep vein thrombosis	47 (0.5)	41 (0.3)	.03	30 (0.5)	22 (0.4)	.27
Pulmonary embolism	100 (1.1)	93 (0.8)	.006	67 (1.1)	49 (0.9)	.09
Pneumonia	644 (7.3)	895 (7.4)	.87	399 (6.5)	413 (6.7)	.61
Postoperative shock	10 (0.1)	9 (0.07)	.35	6 (0.1)	≤ 5 (<0.1)	>.10
Length of stay, days, mean (± standard deviation)	16.8 (22.0)	16.2 (23.3)	.047	16.1 (20.2)	16.0 (23.6)	.72

[a] Individuals who received general anesthesia were matched to recipients of regional anesthesia in terms of age, sex, residence (community or long-term care), Charlson score, hospital type, and propensity score.

These findings in this surgical population with dementia expand upon existing literature on postoperative morbidity and mortality associated with anesthesia technique in hip fracture surgery. Prior meta-analyses of randomized controlled trials have demonstrated that RA is associated with some better outcomes for older adults undergoing hip fracture surgery.[17,20,33] Use of RA was associated with lower risk of 30-day mortality than GA in two meta-analyses of randomized controlled trials,[17,20] with odds ratios in the range of 0.6 to 0.7. There were also fewer specific postoperative complications in individuals who received RA than in those who received GA, including lower rates of thromboembolic events[17] and acute confusional state.[17] A meta-analysis of outcomes associated with GA and RA for all types of surgery also reported similar benefits for RA on measures of mortality and morbidity.[19] In the current study, there was no greater risk of specific postoperative complications or mortality associated with GA, suggesting that factors other than anesthesia technique are associated with postoperative outcomes in this population of individuals with dementia.

Observational studies of outcomes associated with anesthesia in hip fractures in older adults with and without dementia have presented conflicting information on the risk of postoperative morbidity and mortality associated with GA. An earlier cohort study involving 9,598

Table 3. Subgroup Analyses of Outcomes Associated with General or Regional Anesthesia in Older Adults with Hip Fractures and Dementia

Subgroup	30-Day Mortality			Any Major Postoperative Complication			Intensive Care Unit Admission		
	General Anesthesia	Regional Anesthesia	*P*-Value	General Anesthesia	Regional Anesthesia	*P*-Value	General Anesthesia	Regional Anesthesia	*P*-Value
Age									
66–75 (n = 612)	21 (6.9)	12 (3.9)	.08	50 (16.3)	38 (12.4)	.15	28 (9.1)	16 (5.2)	.07
76–85 (n = 5,582)	244 (8.7)	248 (8.9)	.85	494 (17.7)	494 (17.7)	>.99	170 (6.1)	137 (4.9)	.05
>85 (n = 6,076)	426 (14.0)	405 (13.3)	.42	621 (20.4)	637 (21.0)	.61	173 (5.7)	106 (3.5)	<.001
Sex									
Female (n = 9,918)	469 (9.5)	433 (8.7)	.20	859 (17.3)	840 (16.9)	.60	273 (5.5)	177 (3.6)	<.001
Male (n = 2,352)	222 (18.9)	232 (19.7)	.59	306 (26.0)	329 (28.0)	.28	98 (8.3)	82 (7.0)	.22
Residence before hip fracture									
Community (n = 5,708)	313 (9.5)	274 (8.3)	.08	640 (19.5)	641 (19.5)	.98	255 (7.8)	178 (5.4)	<.001
Long-term care (n = 6,562)	378 (13.2)	391 (13.7)	.61	525 (18.4)	528 (18.5)	.92	116 (4.1)	81 (2.8)	.01
Charlson score									
No hospitalization (n = 4,980)	261 (10.5)	249 (10.0)	.55	400 (16.1)	395 (15.9)	.84	101 (4.1)	83 (3.3)	.18
0 (n = 4,038)	214 (10.6)	215 (10.6)	.96	339 (16.8)	361 (17.9)	.34	94 (4.7)	73 (3.6)	.10
1 (n = 1,558)	108 (13.9)	88 (11.3)	.13	192 (24.6)	161 (20.7)	.06	60 (7.7)	38 (4.9)	.02
2 (n = 618)	31 (10.0)	42 (13.6)	.17	66 (21.4)	82 (26.5)	.13	26 (8.4)	16 (5.2)	.12
≥3 (n = 1,076)	77 (14.3)	71 (13.2)	.60	168 (21.2)	170 (31.6)	.89	90 (16.7)	49 (9.1)	.002

individuals with hip fracture who underwent surgery between 1983 and 1993 in 20 U.S. hospitals did not find that GA was associated with greater 30-day mortality than RA (adjusted odds ratio = 1.08, 95% confidence interval = 0.84–1.38), and there were no differences in other perioperative complications.[34] That study included individuals with and without dementia, and the overall rates of 30-day mortality associated with GA (4.4%) and RA (5.4%) were much lower than those observed in the current study, emphasizing the susceptibility of individuals with dementia to perioperative morbidity and mortality. A second, single-center study conducted between 2006 and 2008 in a U.S. hospital also failed to find any significant differences between GA and RA in postoperative mortality, morbidity, and hospital costs,[41] although that study was potentially underpowered. The prevalence of dementia was based solely on hospital records for recorded diagnoses, and it is likely that the reported prevalence rate of 10% was an underestimate of true prevalence of dementia in this population. In contrast, a more-recent observational study involving 18,158 individuals with hip fractures from 126 hospitals in New York State found that RA was associated with a lower rate of in-hospital mortality (2.1%) than GA (2.5%, adjusted odds ratio = 0.71, $P = .01$) and with lower rates of some pulmonary complications.[18] Approximately 20% of the study sample had underlying dementia, which was more common in individuals who received RA. The results of this study are in keeping with other published observational studies that indicate that GA and RA are associated with similar occurrences of adverse outcomes after hip fracture surgery.

There may be additional reasons for selecting RA over GA for surgical procedures in older adults with dementia when possible. Older adults with dementia are particularly susceptible to adverse cognitive outcomes after surgery,[11] and GA has been associated with greater risk of postoperative cognitive dysfunction than RA.[42,43] Older adults with dementia may be particularly prone to other cognitive complications such as delirium,[13,44] and it has also been hypothesized that GA promotes Alzheimer's disease pathology.[45] An observational study of postoperative delirium associated with GA and RA in older adults undergoing hip replacement or hip fracture surgery did not find a greater risk of delirium associated with GA than RA for the entire study population or in subgroup analyses of individuals with cognitive impairment.[46] Some inhalational agents used in GA have been associated with Alzheimer's disease pathology, including greater accumulation of beta-amyloid[47] and hyperphosphorylated tau proteins.[48] Evidence of the promotion of Alzheimer's disease pathology associated with GA from observational studies of humans has not found consistent associations between GA and dementia.[49–52] The few randomized controlled studies in this area have not demonstrated a consistently greater risk of dementia with GA.[53] Therefore, determining whether GA is associated with greater risk of adverse cognitive outcomes than RA requires additional research.

The current study has several strengths. A large, population-based group of older adults with hip fractures and dementia was included, which should generalize to most hip fracture populations in similar settings. The study design used propensity scores to limit potential confounding for many variables that might have been associated with selection of anesthesia technique and postoperative outcomes, increasing the likelihood that confounding did not bias the observed results. Also, subgroup analyses allowed particular individuals with hip fractures and dementia who may have been particularly susceptible to adverse postoperative outcomes to be identified.

There are also several study limitations that merit consideration. The first limitation was the observational study design. Although it was attempted to control for measured confounders, there is the possibility that some factors

associated with selection of anesthesia and subsequent outcomes were imbalanced in the two exposure groups, which could have resulted in biased estimates of the association between anesthesia technique and subsequent outcomes. The databases provide information only on the category of anesthesia administered for surgery. There are a variety of medications that can be administered with GA or RA, and it was not possible to evaluate the effects of specific anesthetic agents on outcomes in this observational study. In addition, detailed information about the severity of cognitive impairment or functional impairment was not available, although an attempt was made to control for these factors by using proxy measures such as residence in LTC and markers of dementia severity. Finally, postoperative cognitive outcomes such as delirium were not included in the study because this has been examined in previous studies,[46] and the measurement of delirium in administrative databases greatly underestimates the true prevalence of delirium reported in prospective studies.[54]

In conclusion, in older adults with hip fracture and dementia the type of anesthesia used during surgery was not associated with 30-day mortality, postoperative medical complications, or hospital LOS. A slightly greater risk of ICU admission was associated with receipt of GA than RA, although the clinical importance of this finding is questionable. Overall, older adults with dementia who undergo surgery for hip fracture have high rates of postoperative morbidity and mortality, highlighting the importance of preventing hip fracture and identifying strategies other than the selection of anesthesia to improve outcomes. Further studies are required to optimize the perioperative care of the growing number of older adults with dementia who will undergo hip fracture repair and other surgical procedures in the future.

ACKNOWLEDGMENTS

This work was supported by Team Grant OTG-88591 from the Canadian Institutes of Health Research (CIHR), Institute of Nutrition, Metabolism, and Diabetes and by Interdisciplinary Capacity Enhancement Grant (HOA-80075) from the CIHR Institute of Gender and Health and the CIHR Institute of Aging. Dr. Seitz is supported by a Clinician Scientist Development Award at Queen's University. Dr. Gill is supported by a CIHR New Investigator Award. Dr. Austin is supported by a Career Investigator Award from the Heart and Stroke Foundation of Ontario. Dr. Gruneir is partially supported by CIHR Team Grant OTG-88591. This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper. Dr. Seitz has received honoraria from Eli-Lilly Canada for participating on an advisory board.

Author Contributions: All authors have contributed to the conception and design of the study, provided revisions to the manuscript, and approved the final submitted manuscript. DPS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Sponsor's Role: None.

REFERENCES

1. Thies W, Bleiler L. Alzheimer's disease facts and figures Alzheimer's Association. Alzheimers Dement 2013;9:208–245.
2. Zuliani G, Galvani M, Sioulis F et al. Discharge diagnosis and comorbidity profile in hospitalized older patients with dementia. Int J Geriatr Psychiatry 2012;27:313–320.
3. Guijarro R, San Román C, Gómez-Huelgas R. Impact of dementia on hospitalization. Neuroepidemiology 2010;35:101–108.
4. Seitz DP, Adunuri N, Gill SS et al. Prevalence of dementia and cognitive impairment among older adults with hip fractures. J Am Med Dir Assoc 2011;12:556–564.
5. Gleason LJ, Menzies IB, Mendelson DA et al. Diagnosis and treatment of osteoporosis in high-risk patients prior to hip fracture. Geriatr Orthop Surg Rehabil 2012;3:79–83.
6. Tysiewicz-Dudek M, Pietraszkiewicz F, Drozdzowska B. Alzheimer's disease and osteoporosis: Common risk factors or one condition predisposing to the other? Ortop Traumatol Rehabil 2007;10:315–323.
7. Van Doorn C, Gruber-Baldini AL, Zimmerman S et al. Dementia as a risk factor for falls and fall injuries among nursing home residents. J Am Geriatr Soc 2003;51:1213–1218.
8. Tinetti ME, Kumar C. The patient who falls: "It's always a trade-off". JAMA 2010;303:258–266.
9. Cree M, Soskolne C, Belseck E et al. Mortality and institutionalization following hip fracture. J Am Geriatr Soc 2000;48:283–288.
10. Laditka JN, Laditka SB, Cornman CB. Evaluating hospital care for individuals with Alzheimer's disease using inpatient quality indicators. Am J Alzheimers Dis 2005;20:27–36.
11. Lee HB, Mears SC, Rosenberg PB et al. Predisposing factors for postoperative delirium after hip fracture repair in individuals with and without dementia. J Am Geriatr Soc 2011;59:2306–2313.
12. Robinson TN, Raeburn CD, Tran ZV et al. Postoperative delirium in the elderly: Risk factors and outcomes. Ann Surg 2009;249:173–178.
13. Kalisvaart K, Vreeswijk R, de Jonghe J et al. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: Implementation and validation of a medical risk factor model. J Am Geriatr Soc 2006;54:817–822.
14. Juliebø V, Bjøro K, Krogseth M et al. Risk factors for preoperative and postoperative delirium in elderly patients with hip fracture. J Am Geriatr Soc 2009;57:1354–1361.
15. Hu C-J, Liao C-C, Chang C-C et al. Postoperative adverse outcomes in surgical patients with dementia: A retrospective cohort study. World J Surg 2012;36:2051–2058.
16. Bail K, Berry H, Grealish L et al. Potentially preventable complications of urinary tract infections, pressure areas, pneumonia, and delirium in hospitalised dementia patients: Retrospective cohort study. BMJ Open 2013; 3(6):pii:e002770. doi: 10.1136/bmjopen-2013-02770.
17. Parker M, Handoll H, Griffiths R. Anaesthesia for hip fracture surgery in adults. Cochrane Database Syst Rev 2004;4:CD000521.
18. Neuman MD, Silber JH, Elkassabany NM et al. Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. Anesthesiology 2012;117:72–92.
19. Rodgers A, Walker N, Schug S et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: Results from overview of randomised trials. BMJ 2000;321:1493.
20. Urwin S, Parker M, Griffiths R. General versus regional anaesthesia for hip fracture surgery: A meta-analysis of randomized trials. Br J Anaesth 2000;84:450–455.
21. Marrie T, Durant H, Kwan C. Nursing home-acquired pneumonia. A case-control study. J Am Geriatr Soc 1986;34:697–702.
22. Beloosesky Y, Grinblat J, Epelboym B et al. Functional gain of hip fracture patients in different cognitive and functional groups. Clin Rehabil 2002;16:321–328.
23. Levy A, O'Brien B, Sellors C et al. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2002;10:67–71.

24. Williams J, Young W. A Summary of Studies on the Quality of Health Care Administrative Databases in Canada. Patterns of Health Care in Ontario: The ICES Practice Atlas, 2nd Ed. Ottawa: Canadian Medical Association, 1996.
25. Seitz DP, Gill SS, Gruneir A et al. Effects of cholinesterase inhibitors on postoperative outcomes of older adults with dementia undergoing hip fracture surgery. Am J Geriatr Psychiatry 2011;19:803–813.
26. Gill SS, Bronskill SE, Normand S-LT et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 2007;146:775–786.
27. Richards J, Brown A, Homan C. The Data Quality Study of the Canadian Discharge Abstract Database. Proceedings of Statistics Canada Symposium, 2001.
28. Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–383.
29. Quan H, Sundararajan V, Halfon P et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–1139.
30. Starfield B, Weiner J, Mumford L et al. Ambulatory care groups: A categorization of diagnoses for research and management. Health Serv Res 1991;26:53–74.
31. Schneeweiss S, Seeger JD, Maclure M et al. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol 2001;154:854–864.
32. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: A study of consistency of ratings. Anesthesiology 1978;49:239–243.
33. Luger T, Kammerlander C, Gosch M et al. Neuroaxial versus general anaesthesia in geriatric patients for hip fracture surgery: Does it matter? Osteoporos Int 2010;21(Suppl 4):S555.
34. O'Hara DA, Duff A, Berlin JA et al. The effect of anesthetic technique on postoperative outcomes in hip fracture repair. Anesthesiology 2000;92:947–957.
35. Scales DC, Guan J, Martin CM et al. Administrative data accurately identified intensive care unit admissions in Ontario. J Clin Epidemiol 2006;59:802–807.
36. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: A Monte Carlo study. Stat Med 2007;26:734–753.
37. Austin PC. Comparing paired vs non-paired statistical methods of analyses when making inferences about absolute risk reductions in propensity-score matched samples. Stat Med 2011;30:1292–1301.
38. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150–161.
39. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–3107.
40. Austin PC. Type I error rates, coverage of confidence intervals, and variance estimation in propensity-score matched analyses. Int J Biostat 2009;5: Article 13.
41. Le-Wendling L, Bihorac A, Baslanti TO et al. Regional anesthesia as compared with general anesthesia for surgery in geriatric patients with hip fracture: Does it decrease morbidity, mortality, and health care costs? Results of a single-centered study. Pain Med 2012;13:948–956.
42. Rasmussen L, Johnson T, Kuipers HM et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003;47:260–266.
43. Papaioannou A, Fraidakis O, Michaloudis D et al. The impact of the type of anaesthesia on cognitive status and delirium during the first postoperative days in elderly patients. Eur J Anaesthesiol 2005;22:492–499.
44. Dyer C, Ashton C, Teasdale T. Postoperative delirium. A review of 80 primary data-collection studies. Arch Intern Med 1995;155:461–465.
45. Scott DA, Silbert BS, Evered LA. Anesthesia and Alzheimer's disease: Time to wake up!. Int Psychogeriatr 2013;1:1–4.
46. Slor CJ, de Jonghe JF, Vreeswijk R et al. Anesthesia and postoperative delirium in older adults undergoing hip surgery. J Am Geriatr Soc 2011;59:1313–1319.
47. Xie Z, Dong Y, Maeda U et al. The common inhalation anesthetic isoflurane induces apoptosis and increases amyloid β protein levels. Anesthesiology 2006;104:988–994.
48. Planel E, Richter KE, Nolan CE et al. Anesthesia leads to tau hyperphosphorylation through inhibition of phosphatase activity by hypothermia. J Neurosci 2007;27:3090–3097.
49. Seitz D, Shah P, Herrmann N et al. Exposure to general anesthesia and risk of Alzheimer's disease: A systematic review and meta-analysis. BMC Geriatr 2011;11:83.
50. Chen C-W, Lin C-C, Chen K-B et al. Increased risk of dementia in people with previous exposure to general anesthesia: A nationwide population-based case–control study. Alzheimers Dement 2014;10:196–204.
51. Sprung J, Jankowski CJ, Roberts RO et al. Anesthesia and incident dementia: A population-based, nested, case-control study. Mayo Clin Proc 2013;88:552–561.
52. Seitz DP, Reimer CL, Siddiqui N. A review of epidemiological evidence for general anesthesia a risk factor for Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 2012;47:122–127.
53. Liu Y, Pan N, Ma Y et al. Inhaled sevoflurane may promote progression of amnestic mild cognitive impairment: A prospective, randomized parallel-group study. Am J Med Sci 2013;345:355–360.
54. Katznelson R, Djaiani G, Tait G et al. Hospital administrative database underestimates delirium rate after cardiac surgery. Can J Anaesth 2010;57:898–902.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Physician diagnostic codes for physician diagnosed dementia.

Please note: Wiley-Blackwell is not responsible for the content, accuracy, errors, or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

Can J Anesth/J Can Anesth (2015) 62:356–368
DOI 10.1007/s12630-015-0315-1

REPORTS OF ORIGINAL INVESTIGATIONS

Combined general and neuraxial anesthesia *versus* general anesthesia: a population-based cohort study

Anesthésie combinée neuraxiale et générale contre anesthésie générale: étude de cohorte basée sur la population

Danielle M. Nash, PhD · Reem A. Mustafa, MD, PhD · Eric McArthur, MSc · Duminda N. Wijeysundera, MD, PhD · J. Michael Paterson, MSc · Sumit Sharan, MD · Christopher Vinden, MD · Ron Wald, MPH · Blayne Welk, MD · Daniel I. Sessler, MD · P. J. Devereaux, MD, PhD · Michael Walsh, MD, PhD · Amit X. Garg, MD, PhD

Received: 4 July 2014 / Accepted: 12 January 2015 / Published online: 27 January 2015

Abstract

Purpose *To determine whether combining spinal or epidural anesthesia with general anesthesia (combined anesthesia) reduces major medical complications of elective surgery compared with general anesthesia alone.*

Methods *We conducted a propensity-matched population-based historical cohort study using large healthcare databases from Ontario, Canada. We identified patients undergoing 21 different elective procedures that were amenable to either combined anesthesia or general anesthesia alone in 108 hospitals from 2004 to 2011. We assessed the following four outcomes together as a composite and individually in the 30 days following surgery: acute kidney injury, stroke, myocardial infarction, and all-cause mortality.*

Results *Prior to matching, we identified 21,701 patients receiving general anesthesia and 8,042 patients receiving combined anesthesia. After matching, our cohort included*

Author contributions *Danielle M. Nash, Reem A. Mustafa, Sumit Sharan,* and *Amit X. Garg* helped design the study. *Duminda N. Wijeysundera* contributed to the study design by suggesting operations to focus on and administrative codes/variables to use for the study. *J. Michael Paterson* contributed to the study design by suggesting administrative codes to use for anesthesia type. *Christopher Vinden* contributed to the study design by suggesting administrative codes to use to identify epidural insertions. *Ron Wald* contributed to the study design by providing clinical expertise regarding acute kidney injury. *Blayne Welk* contributed to the study design by suggesting the additional outcome of length of stay. *P.J. Devereaux* contributed to the study design by adding clinical expertise regarding cardiovascular events. *Reem A. Mustafa* developed the preliminary protocol, and *Danielle M. Nash* completed the study protocol. *Danielle M. Nash, Reem A. Mustafa, Eric McArthur, Duminda N. Wijeysundera, J. Michael Paterson, Christopher Vinden, Ron Wald, Blayne Welk, P.J. Devereaux,* and *Amit X. Garg* contributed to the interpretation of results. *Daniel I. Sessler* contributed to the interpretation of results particularly regarding discussion about intraoperative *vs* postoperative anesthesia use. *Michael Walsh* contributed to the interpretation of results particularly regarding the limitations of the study. *Sumit Sharan* contributed to the interpretation of the results through a dialogue regarding standard practice for epidural catheter insertions. *Danielle M. Nash* initiated and finalized the manuscript. *Reem A. Mustafa, Eric McArthur, Duminda N. Wijeysundera, J. Michael Paterson, Ron Wald, Blayne Welk, Daniel I. Sessler, P.J. Devereaux, Michael Walsh,* and *Amit X. Garg* contributed to the manuscript writing. *Eric McArthur* had access to the individual level data for the study and completed all the study analyses. *Sumit Sharan* and *Christopher Vinden* reviewed the final manuscript. *Amit X. Garg* provided study oversight and supervision to Ms. Nash.

D. M. Nash, PhD (✉) · E. McArthur, MSc · J. M. Paterson, MSc
Institute for Clinical Evaluative Sciences Western, London Health Sciences Centre, 800 Commissioners Rd. E, Room ELL-113A, London, ON N6A 4G5, Canada
e-mail: danielle.nash@ices.on.ca

R. A. Mustafa, MD, PhD
Department of Medicine, University of Missouri-Kansas City, Kansas City, MO, USA

D. N. Wijeysundera, MD, PhD
Li Ka Shing, Knowledge Institute of St. Michael's Hospital, Toronto, ON, Canada

S. Sharan, MD
Department of Anaesthesia, Health Sciences North, Sudbury, ON, Canada

C. Vinden, MD · B. Welk, MD
Department of Surgery, Western University, London, ON, Canada

12,379 patients. Twenty-eight baseline characteristics were well-matched between the combined (n = 4,773) and general anesthesia groups (n = 7,606). Mean patient age was 66 yr. Relative to general anesthesia alone, combined anesthesia was not associated with a reduced risk for the composite outcome [104/4,773 (2.2%) vs 162/7,606 (2.1%); odds ratio (OR) 0.97; 95% confidence interval (CI) 0.75 to 1.24] or for any of the four component outcomes when examined separately: acute kidney injury (OR 0.93; 95% CI 0.58 to 1.51), stroke (OR 0.79; 95% CI 0.36 to 1.73), myocardial infarction (OR 1.04; 95% CI 0.69 to 1.57), and all-cause mortality (OR 0.91; 95% CI 0.59 to 1.42).

Conclusion *The addition of spinal or epidural anesthesia to general anesthesia was not associated with a reduced risk of major medical complications among 21 different elective procedures when compared with general anesthesia alone.*

Résumé

Objectif *Déterminer si la combinaison d'une rachianesthésie ou d'une anesthésie péridurale avec une anesthésie générale (anesthésie combinée) diminue les complications médicales majeures d'une chirurgie programmée comparativement à une anesthésie générale seule.*

Méthodes *Nous avons réalisé une étude de cohorte historique basée sur une population appariée pour la propension en utilisant les grandes bases de données de soins de santé de la province d'Ontario (Canada). Nous avons identifié des patients subissant 21 types différents de procédures chirurgicales programmées qui étaient susceptibles de bénéficier d'une anesthésie combinée ou d'une anesthésie générale seule dans 108 hôpitaux entre 2004 et 2011. Nous avons évalué les quatre aboutissements suivants ensemble sous forme de critère composite et individuellement, dans les 30 jours suivant l'intervention: insuffisance rénale aiguë, accident vasculaire cérébral (AVC), infarctus du myocarde et mortalité toute cause.*

Résultats *Avant l'appariement, nous avons identifié 21 701 patients ayant reçu une anesthésie générale et 8 042 patients ayant reçu une anesthésie combinée. Après l'appariement, notre cohorte incluait 12 379 patients. Vingt-huit caractéristiques à l'inclusion étaient bien appariées entre les groupes « anesthésie combinée » (n = 4 773) et « anesthésie générale » (n = 7 606). L'âge moyen des patients était de 66 ans. Par rapport à l'anesthésie générale seule, l'anesthésie combinée n'a pas été associée à une réduction du risque pour le critère d'évaluation composite [104/4 773 (2,2 %) contre 162/7 606 (2,1 %); rapport de cotes (OR) 0,97; intervalle de confiance (IC) à 95 %: 0,75 à 1,24] ou à l'un des quatre éléments du critère d'évaluation quand ils étaient calculés séparément: insuffisance rénale aiguë (OR: 0,93; IC à 95 %: 0,58 à 1,51), AVC (OR: 0,79; IC à 95 %: 0,36 à 1,73), infarctus du myocarde (OR: 1,04; IC à 95 %: 0,69 à 1,57) et mortalité toute cause (OR: 0,91; IC à 95 %: 0,59 à 1,42).*

Conclusion *L'ajout de la rachianesthésie ou de l'anesthésie péridurale à l'anesthésie générale n'a pas été associé à une diminution du risque de complications médicales majeures pour 21 procédures chirurgicales électives différentes par rapport à l'anesthésie générale administrée seule.*

Neuraxial anesthesia (epidural and spinal anesthesia) is widely used for major surgery in combination with general anesthesia. It has shown advantages over general anesthesia alone, including better postoperative pain control, fewer postoperative respiratory difficulties, and faster return of regular gastrointestinal function.[1-6] Furthermore, use of epidural anesthesia in combination with general anesthesia or on its own may slightly improve survival in patients having major surgery.[7] Nevertheless, the impact of combining neuraxial anesthesia with general anesthesia on mortality and other adverse postoperative medical complications, including acute kidney injury and myocardial infarction, remains uncertain. Uncertainty remains in part because previous studies did not differentiate between neuraxial anesthesia alone *vs* the combination of neuraxial and general anesthesia.[5,8-10] Contrary to other research findings, a *post hoc* analysis of patients at high risk for cardiovascular complications in the POISE trial showed that patients who received neuraxial blockade were actually at greater risk for cardiovascular complications.[10] We therefore conducted a large population-based study to explore this

R. Wald, MPH
Department of Medicine, University of Toronto, Toronto, ON, Canada

D. I. Sessler, MD
Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

P. J. Devereaux, MD, PhD · M. Walsh, MD, PhD
Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada

A. X. Garg, MD, PhD
Department of Medicine, Western University, London, ON, Canada

area further and to determine if the use of neuraxial anesthesia combined with general anesthesia (combined anesthesia) is associated with lower rates of acute kidney injury, myocardial infarction, stroke, and mortality compared with general anesthesia alone. Specifically, we tested the primary hypothesis that patients receiving combined anesthesia would have lower risk of a composite outcome, including acute kidney injury, myocardial infarction, stroke, or mortality compared with patients receiving only general anesthesia. We also tested the secondary hypotheses that risk of pneumonia would be reduced and hospital length of stay post-surgery would be shorter for patients who received combined anesthesia than for those who received general anesthesia alone.

Methods

Setting and study design

Residents of Ontario, Canada (2012 population: 13,505,900) have universal access to hospital care and physician services, and these encounters are recorded in large population-based healthcare databases which are linked using unique encoded identifiers and held at the Institute for Clinical Evaluative Sciences (ICES; www.ices.on.ca). Using these data sources, we conducted a propensity-matched population-based historical cohort study at the ICES Western site in London, Ontario, Canada. This study was approved by the Sunnybrook Health

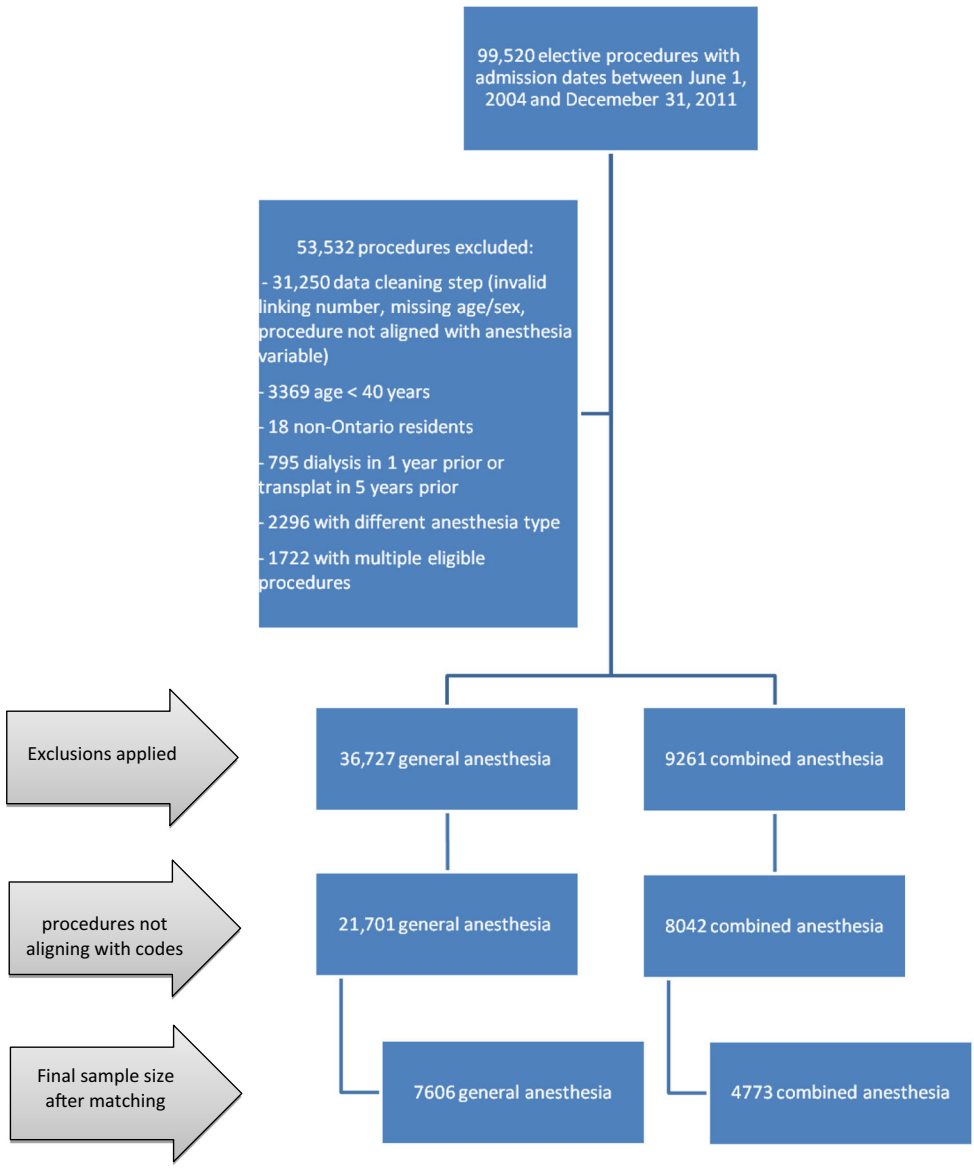

Figure Participant flow diagram

Sciences Centre Research Ethics Board in Toronto, Ontario, Canada. Written informed patient consent was not required for this study. The reporting of this study follows guidelines for observational studies.[11]

Data sources

We obtained data for our study from five linked healthcare administrative databases which we have used in prior studies of perioperative medicine.[12-14] Diagnostic and procedural information for all hospitalizations are recorded in the Canadian Institute for Health Information's Discharge Abstract. From 2002 onwards, the International Statistical Classification of Diseases and Related Health Problems—Tenth Revision, Canada (ICD-10-CA) was used to record all diagnostic codes, and the Canadian Classification of Health Interventions was used to record all procedural codes. We used the latter database to select major elective surgeries for study inclusion. Health claims for inpatient and outpatient physician services are recorded in the Ontario Health Insurance Plan Claims History Database where claims lead to physician reimbursement. The ICES Physician Database has information on all physicians practicing in Ontario, including demographics and educational background. The Registered Persons Database (RPDB) contains demographic and vital status information for all persons eligible to receive insured health services in Ontario. The Ontario Drug Benefits (ODB) program provides prescription drug coverage to all residents of Ontario who are 65 yr of age or older. The ODB database records prescription characteristics, including the drug identification number, the number of days supplied, and the date the prescription was filled. We used this database to ascertain drug prescriptions for a subset of our cohort aged 65 yr and older.

Exposure categorization

We identified elective daytime procedures performed from June 1, 2004 to December 31, 2011 that were amenable to the use of either neuraxial anesthesia combined with general anesthesia or general anesthesia alone. In a preliminary assessment, we carefully reviewed 960 different major surgical procedures and identified 21 where combined anesthesia and general anesthesia were each used in at least 100 cases. These 21 procedures were categorized into five main procedure types: 1) aorta and peripheral vascular disease, 2) bladder, 3) bowel, 4) lung, and 5) other gastrointestinal (described in Table 1). We excluded procedures with the following patient characteristics: non-Ontario residents, age younger than 40 yr, end-stage renal disease prior to surgery (as the assessment of acute kidney injury after surgery is no longer relevant), and an anesthesia type other than combined neuraxial and general anesthesia or general anesthesia alone. For patients with multiple eligible procedures during the study period, we randomly chose one procedure for study inclusion.

We used the intervention anesthesia technique variable from inpatient hospital records to define our exposure groups. Patients receiving procedures using combined anesthesia (spinal or epidural combined with general) were compared with patients receiving procedures using general anesthesia alone. We then confirmed the use of neuraxial anesthesia using fee-for-service codes for epidural and spinal anesthesia that are billed for physician reimbursement in Ontario and further excluded any procedures where these codes did not align with the hospital anesthesia technique variable. We also conducted *post hoc* analyses, which showed that more than half of the participants in the combined anesthesia group had received a physician billing code for postoperative pain management (Appendix A).

Outcome measures

We assessed the risk of the following four medical outcomes together as a composite (primary outcome) and individually: acute kidney injury, stroke, myocardial infarction, and all-cause mortality (secondary outcomes). Acute kidney injury, stroke, and myocardial infarction were identified through validated hospital diagnostic codes (including any codes during hospital readmission) in the 30 days following the surgery.[15,16] All-cause mortality was identified through the RPDB. We identified our composite outcome *a priori*. Our primary outcome met the three criteria of a valid composite outcome: 1) outcomes are of similar importance to patients; 2) all endpoints occur with similar frequency; and 3) endpoints are likely to have similar risk reductions.[17] As a preliminary analysis, we examined consistency of the anesthesia effect across the four individual component outcomes using a test for heterogeneity and determined that it was appropriate to create a composite outcome.[18]

As additional *post hoc* analyses, we looked at outcomes of hospitalization with pneumonia in the 30 days post-surgery and length of stay for the index surgery. We also compared the distributions of length of stay for each procedure type between patients who received combined *vs* general anesthesia. The coding definitions for our study outcomes and reported validity are presented in Appendix B.

Subgroup analyses

We conducted two *post hoc* subgroup analyses to assess the following hypotheses: 1) patients who are at high cardiovascular risk or currently have cardiovascular

Table 1 Procedures selected for inclusion in our study that are amenable to both combined anesthesia (general with neuraxial) and general anesthesia alone

Procedure Category	Procedure Description	Total *n*
Aorta & Peripheral Vascular Disease	Abdominal aorta repair using open approach with synthetic material (e.g., Teflon felt, Dacron, Nylon, Orlon).	1,488
	Abdominal aorta bypass using synthetic material; bypass terminating at lower limb vessels (e.g., iliac, femoral, popliteal, tibial).	1,461
	Arteries of leg bypass not elsewhere classified using autograft (e.g., saphenous vein); bypass terminating in lower limb artery (e.g., femoropopliteal).	802
Bladder	Radical bladder excision with creation of continent urinary reservoir and permanent cutaneous stoma.	386
	Radical bladder excision using open approach.	447
Bowel	Partial large intestine excision using open approach; enterocolostomy anastomosis technique.	1,475
	Partial large intestine excision using open approach; colocolostomy anastomosis technique.	362
	Partial large intestine excision open approach; colorectal anastomosis technique.	1,568
	Reattachment of the large intestine; open approach of colostomy (may involve: reanastomosis of colon to [Hartmann] rectal stump or mucous fistula).	2,055
	Partial large intestine excision using endoscopic (laparoscopic, laparoscopic-assisted, hand-assisted) approach; enterocolostomy anastomosis technique.	2,631
	Small intestine bypass with exteriorization using open approach; end enterostomy (e.g., terminal, end, or loop ileostomy).	3,525
	Partial large intestine excision using endoscopic (laparoscopic, laparoscopic-assisted, hand-assisted) approach; colocolostomy anastomosis technique.	2,070
	Partial large intestine excision using open approach; stoma formation with distal closure.	703
Lung	Total lobe of lung excision using open thoracic approach.	911
	Partial lobe of lung excision using open thoracic approach.	352
	Partial lung excision not elsewhere classified using open thoracic approach.	270
Other Gastrointestinal	Abdominal cavity release using open approach using device not elsewhere classified.	4,414
	Partial liver excision using open approach.	3,873
	Partial abdominal cavity excision using open approach.	301
	Partial stomach excision without vagotomy using open approach; gastrojejunal (or gastroenteral not elsewhere classified [NEC]) anastomosis.	316
	Partial pancreas excision with duodenum without vagotomy using open approach.	333

disease will be more likely to experience the composite outcome if they received combined anesthesia *vs* general anesthesia, and 2) the effect of anesthesia type on our composite outcome decreases over time. For the first *post hoc* subgroup analysis, we defined high cardiovascular risk as patients who experienced at least one of the following comorbidities at baseline: 1) stroke, 2) coronary artery disease, 3) congestive heart failure, 4) hypertension, or 5) diabetes. This is based on risk factors described by the American Heart Association.[19] For the second analysis, we separated our study into two time periods: 2004-2007 and 2008-2011.

Statistical analysis

We performed all statistical analyses using SAS® 9.2 (SAS Institute Incorporated, Cary, NC, USA, 2008). For baseline characteristics, means and standard deviations were calculated for continuous variables and frequencies and proportions were calculated for binary and categorical variables. Baseline characteristics for participants in the general anesthesia group are shown without and with weighting. This weighting technique was used to account for the variable 1:1 and 1:2 matches (described below). Patient characteristics were compared between the combined and general anesthesia groups using the standardized difference, a measure used to describe differences between group means relative to the pooled standard deviation and indicates a meaningful difference if it is greater than 10%.[20]

We used a propensity score matched design to balance the distribution of potential confounding variables between our two groups.[21] Propensity scores were derived in a logistic regression model (predicting receipt of combined

anesthesia) and included 28 baseline characteristics identified *a priori* as potential confounders: age; sex; neighbourhood median household income quintile; procedure type (based on individual procedure code); year of surgery; academic (*vs* community) hospital; small community hospital (defined as a hospital in a community with fewer than 10,000 residents), number of primary care physician visits in previous year; number of cardiologist consultations in previous year; a history of stroke, chronic kidney disease, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, hypertension, diabetes, and previous cardiovascular procedures (carotid ultrasound, coronary angiogram, coronary revascularization, echocardiography, holter monitor, stress test) in the previous five years; and for those aged 66 yr or older, prescription for an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, statin, or diuretic in the previous 120 days (for patients < 66 yr old without available data, this was coded as no drug prescriptions). The estimated glomerular filtration rate (eGFR) value within $\pm$ 10 mL·min^{-1} per 1.73 m^2 was also included in the propensity score if a baseline serum creatinine value was available through laboratory data that we previously linked to the administrative data sources (participants without available data were matched to each other).

Each combined anesthesia procedure was matched to one or two general anesthesia procedures (i.e., variable matches of 1:1 and 1:2 based on the number of available matches). We matched on procedure codes where the standardized differences between exposure groups were greater than 20% prior to matching. This included large intestine excision, total lung excision, and abdominal aorta bypass. We also matched on age ($\pm$ two years), sex, procedure date ($\pm$ six months), chronic kidney disease, coronary artery disease, eGFR value ($\pm$ 10 mL·min^{-1} per 1.73 m^2; if laboratory data were available), and propensity score ($\pm$ 0.2 $\times$ standard deviation of the logit).

We performed conditional logistic regression analyses for our composite outcome, four separate secondary outcomes, the additional outcome of pneumonia, and the *post hoc* subgroup analyses. We reported odds ratios and calculated associated 95% confidence intervals (CIs). Based on the low incidence of the outcomes, the odds ratios approximate risk ratios and can be interpreted as such. For our additional outcome of length of stay, we assessed differences between groups using a Wilcoxon signed-rank test accounting for the matched design and non-normal distribution of the data.[22] We used a Wilcoxon-Mann-Whitney test to compare the distributions of length of stay for patients who received combined anesthesia *vs* general anesthesia for each procedure type.

Results

There were 99,520 procedures that met our inclusion criteria (see Figure for participant flow diagram). After applying our exclusions, there were 8,042 combined anesthesia procedures and 21,701 general anesthesia procedures. Our final sample size after matching was 12,379 patients (4,773 combined and 7,606 general) across 108 Ontario hospitals.

The patient baseline characteristics were very similar between the two anesthesia groups (Table 2). The average patient age was 66 yr, and approximately 46.0% of the patients were female. The majority of the included study procedures were bowel (35.0%) or other gastrointestinal (43.7%). The patient cohort had relatively high rates of hypertension (59.3%) and diabetes (23.6%). Over half of the cohort was over 65 yr of age and had available data on medication use. Of these patients, 46.2% were prescribed an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and 41.6% were prescribed a statin in the 120 days prior to the surgery.

The outcomes are presented in Table 3. Relative to general anesthesia alone, combined anesthesia was not associated with a lower risk of the primary composite outcome [104/4,773 (2.2%) *vs* 162/7,606 (2.1%); odds ratio (OR) 0.97; 95% CI 0.75 to 1.24] or any of the four secondary outcomes when examined separately: acute kidney injury (OR 0.93; 95% CI 0.58 to 1.51); stroke (OR 0.79; 95% CI 0.36 to 1.73); myocardial infarction (OR 1.04; 95% CI 0.69 to 1.57); and all-cause mortality (OR 0.91; 95% CI 0.59 to 1.42). The odds ratio was homogeneous ($P = 0.88$) in all four components of the composite outcome. There was no significant difference between combined and general anesthesia groups for the additional outcome of pneumonia (OR 1.28; 95% CI 0.90 to 1.83); however, there was a significant difference for the outcome of length of stay between combined and general anesthesia groups (median seven days; interquartile range, IQR [5-8] *vs* median six days; IQR [5-8], respectively; $P = 0.001$). We also present the length of stay distributions for each procedure type comparing combined anesthesia with general anesthesia (Appendix C). We found significantly longer hospital length of stay based on the distribution of combined anesthesia *vs* general anesthesia for the following seven procedures: radical bladder excision with creation of a continent urinary reservoir and a permanent cutaneous stoma, radical bladder excision using the open approach, reattachment of the large intestine using the open approach of colostomy, partial large intestine excision using the endoscopic approach, small intestine bypass with exteriorization using the open approach, abdominal cavity release using the open

Table 2 Patient baseline characteristics after matching for patients receiving combined anesthesia (general with neuraxial) compared with patients receiving general anesthesia alone

Baseline Characteristic	Combined	General		Standardized Difference
		Without Weighting	With Weighting*	
Total	$n = 4{,}773$	$n = 7{,}606$	$n = 4{,}773$	
Demographics				
Age at surgery, mean (SD)	66.65 (10.72)	66.27 (10.78)	66.65(8.49)	0.00
Female	2,149 (45.0%)	3,527 (46.4%)	2,149 (45.0%)	0.00
Neighborhood income quintile:				
1 (lowest)	883 (18.5%)	1,364 (17.9%)	860 (18.0%)	0.01
2	905 (18.9%)	1,564 (20.6%)	968 (20.3%)	0.03
3 (middle)	996 (20.8%)	1,552 (20.4%)	980 (20.5%)	0.01
4	986 (20.6%)	1,582 (20.8%)	1,005 (21.1%)	0.01
5 (highest)	1,003 (21.0%)	1,544 (20.3%)	961 (20.1%)	0.02
Procedure factors				
Surgery Type:				
Aorta & peripheral vascular disease	779 (16.3%)	1,040 (13.7%)	749 (15.7%)	0.02
Bowel	1,690 (35.4%)	2,643 (34.8%)	1,649 (34.6%)	0.02
Lung	236 (4.9%)	313 (4.1%)	231 (4.8%)	0.00
Bladder	96 (2.0%)	175 (2.3%)	102 (2.1%)	0.01
Other gastrointestinal	1,972 (41.3%)	3,435 (45.2%)	2,043 (42.8%)	0.03
Academic hospital	1,128 (23.6%)	1,581 (20.8%)	1,061 (22.2%)	0.03
Small/rural hospital	446 (9.3%)	818 (10.8%)	487 (10.2%)	0.03
Healthcare access in the past 1 year				
Primary care physician visits, mean (SD)	9.68 (8.84)	9.57 (8.68)	9.62 (10.62)	0.01
Cardiologist consults	3,200 (67.0%)	4,891 (64.3%)	3,167 (66.4%)	0.01
Comorbidities in the past 5 years				
Stroke	64 (1.3%)	92 (1.2%)	60 (1.3%)	0.01
Chronic kidney disease	62 (1.3%)	66 (0.9%)	62 (1.3%)	0.00
Coronary artery disease	1,361 (28.5%)	1,979 (26.0%)	1,361 (28.5%)	0.00
Congestive heart failure	276 (5.8%)	440 (5.8%)	290 (6.1%)	0.01
Chronic obstructive pulmonary disease	165 (3.5%)	199 (2.6%)	139 (2.9%)	0.03
Hypertension	2,855 (59.8%)	4,491 (59.0%)	2,864 (60.0%)	0.00
Diabetes mellitus	1,142 (23.9%)	1,783 (23.4%)	1,145 (24.0%)	0.00
Carotid ultrasound	583 (12.2%)	842 (11.1%)	565 (11.8%)	0.01
Coronary angiogram	319 (6.7%)	442 (5.8%)	315 (6.6%)	0.00
Coronary revascularization	177 (3.7%)	242 (3.2%)	174 (3.7%)	0.00
Echocardiography	1,693 (35.5%)	2,571 (33.8%)	1,722 (36.1%)	0.01
Holter monitor	562 (11.8%)	913 (12.0%)	587 (12.3%)	0.02
Stress test	1,743 (36.5%)	2,622 (34.5%)	1,755 (36.8%)	0.01
Medications prescribed in the past 120 days				
Subcohort with available medication data (> 66 yr)	2,711 (56.8%)	4,202 (55.3%)	2,719 (57.0%)	0.00
Angiotensin converting enzyme inhibitor	867 (32.0%)	1,281 (30.5%)	855 (31.5%)	0.01
Angiotensin receptor blocker	430 (15.9%)	614 (14.6%)	406 (14.9%)	0.02
Beta-blockers	750 (27.7%)	1152 (27.4%)	781 (28.7%)	0.02
Statins	1,179 (43.5%)	1,694 (40.3%)	1,148 (42.2%)	0.02
Diuretics	725 (26.7%)	1,087 (25.9%)	709 (26.1%)	0.01

*Weighting was used to account for the variable 1:1 and 1:2 matches

Table 3 Event rates and odds ratios comparing patients receiving combined anesthesia (general with neuraxial) with general anesthesia alone

Outcome	Events		Odds Ratio	95% CI
	Combined (n = 4,773)	General (n = 7,606)*		
Composite (acute kidney injury, stroke, myocardial infarction, or mortality)	104 (2.2%)	162 (2.1%)	0.97[†]	0.75 to 1.24
Acute Kidney Injury	28 (0.6%)	45 (0.6%)	0.93	0.58 to 1.51
Stroke	10 (0.2%)	18 (0.2%)	0.79	0.36 to 1.73
Myocardial Infarction	40 (0.8%)	57 (0.8%)	1.04	0.69 to 1.57
All-Cause Mortality	32 (0.7%)	56 (0.7%)	0.91	0.59 to 1.42
Pneumonia	58 (1.2%)	67 (0.9%)	1.28	0.90 to 1.83
Length of Stay, days; median [IQR]	7 [5-8]	6 [5-8]	N/A	P = 0.0009[‡]

CI = confidence interval; IQR = interquartile range

*General anesthesia is the referent group

[†] The odds ratio is < 1.00 even though the combined group had a slightly higher proportion of composite events than the general (referent group). This occurred because of the weighting technique used to account for variable matching ratios

[‡] For length of stay, this is the P value from a Wilcoxon signed-rank test

approach with a device not elsewhere classified, and partial liver excision using the open approach.

For our *post hoc* subgroup analyses, we did not find any significant differences between anesthesia type and our primary composite outcome when stratified by cardiovascular risk or time period (Appendices D and E).

Discussion

Overall, in our population-based study of over 12,000 patients, we did not observe any associations between combined anesthesia *vs* general anesthesia alone and new-onset acute kidney injury, myocardial infarction, stroke, all-cause mortality, or pneumonia. Duration of hospitalization was statistically significant, with longer length of stay among individuals with combined anesthesia. We further investigated this association by presenting the distributions of length of stay for each procedure type and found a greater length of stay with combined anesthesia for seven of the 21 procedures, which are likely driving this difference. Nevertheless, these findings should be further investigated in future studies, since this analysis was completed *post hoc* and did not account for confounding or multiple testing.

There have been conflicting results regarding the benefits of neuraxial anesthesia. Bignami *et al*. performed a meta-analysis of 33 small randomized clinical trials to compare patient outcomes from surgery involving thoracic epidural anesthesia (whether used alone or in combination; total 1,105 patients) *vs* general anesthesia alone (total 1,231 patients). Their findings showed that the use of thoracic epidural anesthesia resulted in a lower risk of acute kidney injury and a composite outcome of myocardial infarction and mortality.[9] Another meta-analysis of almost 10,000 patients across 141 trials showed a non-significant reduction in both stroke and myocardial infarction with neuraxial anesthesia (used in combination with general anesthesia or alone) compared with general anesthesia alone.[5] Finally, a large *post hoc* analysis of patients at high risk for cardiovascular complications in the POISE trial found that patients who received neuraxial blockade (whether used alone or in combination) compared with general anesthesia alone were actually at greater risk for cardiovascular complications.[10] It thus remains unclear if neuraxial anesthesia is beneficial when combined with general anesthesia or only when used alone. We restricted our analysis to neuraxial anesthesia combined with general anesthesia rather than isolated neuraxial anesthesia, which may partly explain why we did not find a reduction in the development of major medical outcomes. Furthermore, our results may differ from those observed in the analysis of the POISE participants, since the patients in our study were fairly healthy compared with the POISE patients who were at risk for cardiovascular complications.[10] Although, in a *post hoc* analysis of our data concerning a subgroup of patients with cardiovascular risk factors (or with previous cardiovascular events), we did not find any significant differences between anesthesia type and our primary outcome (Appendix D).

A large population-based study conducted in Ontario, Canada by Wijeysundera *et al*. found a small 30-day survival benefit among patients who received epidural anesthesia for non-cardiac procedures, as defined by a

physician billing for an epidural catheter (i.e., could include epidural anesthesia used alone or in combination with other anesthesia types) compared with procedures without epidural anesthesia. The authors concluded that their study does not provide evidence that epidural anesthesia should be used to improve patient survival, but that it is safe to use for other potential benefits.[7] Our study did not show a reduced risk of mortality with neuraxial anesthesia used in combination with general anesthesia. The overall mortality rate for our study was only 0.5% compared with almost 2% in the study by Wijeysundera *et al*.[7] This difference in mortality may be due to differences in the procedures that were selected for study inclusion.

In the past, studies have shown that epidural anesthesia reduced the risk of morbidity or mortality for high-risk operations; however, more recent studies, including randomized controlled trials, have not been able to reproduce such compelling results.[23] A meta-analysis by Pöpping *et al.* showed that the relative benefit of epidural anesthesia to prevent respiratory complications has decreased over the last three decades due to the reduced risk among patients who receive general anesthsia.[4] This may be due to safer surgical practices that may negate any benefits that epidural anesthesia can provide, including shorter-acting general anesthetic drugs, improved monitoring, and less-invasive surgeries.[24] In a *post hoc* subgroup analysis, we looked at the association between anesthesia type and our primary outcome across two different time periods (2004-2007 and 2008-2011) and did not find a significant difference. This is likely because we were looking across a period of only seven years. Large studies may still not have enough statistical power to detect modest improvements in mortality and morbidity with different types of anesthesia should they in truth exist. These considerations may partly explain the lack of association in our study.

Strengths and limitations

Previous studies performed to assess the potential benefits of using neuraxial anesthesia have generally been small clinical trials or cohort studies that focused on only one procedure (e.g., coronary artery bypass graft surgery) or procedures performed at only one hospital. Meta-analyses have been carried out in an attempt to summarize the effect of neuraxial anesthesia on major medical outcomes; however, they have failed to differentiate between neuraxial anesthesia used in combination with general anesthesia and isolated neuraxial anesthesia. It is possible that a sufficiently powered randomized clinical trial will never be conducted on this topic because of the excessive sample size that would be needed to show a modest risk reduction. Our large population-based observational study included all major elective surgeries across 108 Ontario hospitals that were eligible for both general anesthesia combined with neuraxial anesthesia and general anesthesia alone. By expanding our research focus outside of a single-centre or single procedure, we provide results that summarize the overall effect of the addition of neuraxial anesthesia to general anesthesia for major elective surgeries in Ontario. These results are generalizable to other regions with healthcare systems similar to those in Ontario. Furthermore, by limiting our study to only surgeries amenable to either anesthesia type and by utilizing propensity-scores to match on patient factors, we have attempted to reduce potential indication bias. Finally, we compared surgeries using neuraxial anesthesia combined with general anesthesia with surgeries using general anesthesia alone to isolate the effect of the combined anesthesia, which is not apparent in past meta-analyses on this topic.

Relevant to all observational studies, there may have been some residual confounding due to unmeasured and unknown confounders that could have influenced the type of anesthesia used, e.g., the type of catheter used when the neuraxial anesthesia was initiated and the duration of the blockade. Residual confounding may also partly explain our observation of longer duration of hospitalization for patients who received combined anesthesia.

Using our data sources, it is difficult to determine if the neuraxial anesthesia was used during the surgery or in the postoperative period for the management of pain. We conducted *post hoc* analyses which showed that more than half of the participants in the combined anesthesia group had received a physician billing code for postoperative pain management (Appendix A). Therefore, at least half of all participants in the combined group received epidural or spinal anesthesia for postoperative pain control, but it is not known whether they also received neuraxial anesthesia throughout the duration of the surgery. In practice, it is common for the catheter to be inserted prior to the surgery but not used until the post-surgical period to deliver neuraxial anesthesia for pain management. Furthermore, there are benefits to using neuraxial anesthesia during both the perioperative and postoperative periods.[2,6,25,26]

There may have been some misclassification between anesthesia types in our study, but this is likely minimal since we confirmed the anesthesia type defined through the hospital records with the fee-for-service physician codes for epidural catheter insertion and excluded individuals who had a code that did not match with the anesthesia type variable. Another limitation is that we could not separate the use of epidural anesthesia from spinal anesthesia in this study; however, both epidural and spinal anesthesia should demonstrate a signal in the same direction, so this would not explain our lack of associations. For example, in the meta-analysis by Rodgers *et al.*, there were no significant

differences in mortality comparing spinal and epidural anesthesia.[5]

Overall, we found that the addition of spinal or epidural anesthesia to general anesthesia is not associated with a different risk of major medical surgical complications after 21 different elective surgeries when compared with general anesthesia alone.

Acknowledgement We thank Brogan Inc., Ottawa for use of its Drug Product and Therapeutic Class Database.

Conflicts of interest None declared.

Funding This project was conducted at the Institute for Clinical Evaluative Sciences (ICES) site at Western University. The Institute for Clinical Evaluative Sciences is funded by an annual grant from the Ontario Ministry of Health and Long-term Care (MOHLTC). The Institute for Clinical Evaluative Sciences site at Western University is funded by an operating grant from the Academic Medical Organization of Southwestern Ontario (AMOSO). The opinions, results, and conclusions are those of the authors and are independent from the funding sources. No endorsement by ICES, AMOSO, or the MOHLTC is intended or should be inferred. This study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board in Toronto, Ontario, Canada. Written informed patient consent was not required for this study.

Appendix A: *Post hoc* assessment of frequency of postoperative pain management based on physician billing code

When patients received postoperative pain management	*n* (%)
On the day of surgery	2,028 (42.5%)
1 day after	2,818 (59.0%)
2 days after	2,503 (52.4%)
During all 3 days	1,213 (25.4%)

Appendix B: Definitions of acute kidney injury, stroke, myocardial infarction, all-cause mortality, length of stay, and pneumonia using validated diagnostic codes

Outcome	Databases	Codes	Validity
Acute Kidney Injury	CIHI-DAD*	ICD-10-CA: N17[†]	Sensitivity: 22-62%, PPV: 17.3-74.2%[15‡]
Stroke	CIHI-DAD*	ICD-10-CA: G45, H341, I61, I629, I630, I631, I632, I633, I634, I635, I638, I639, I64[†,§]	Sensitivity: 75-81%, PPV: 69-87%[16‡]
Myocardial Infarction	CIHI-DAD*	ICD-10-CA: I21, I22[†,‖]	Sensitivity: 89%, PPV: 87%[16‡]
All-Cause Mortality	RPDB**	Vital status field	Sensitivity: 94%, PPV: 100%[27‡]
LOS	CIHI-DAD*	LOS field	Agreement rates 100% for both admission and discharge dates;[28] agreement 99.9% for LOS[16]
Pneumonia	CIHI-DAD*	ICD10-CA: J12, J13, J14, J15, J16, J17, J18, P23[†,††]	Sensitivity: 80%, PPV: 69%[16‡]

*CIHI-DAD = Canadian Institute for Health Information's Discharge Abstract and Databases

† ICD-10-CA = The International Statistical Classification of Diseases and Related Health Problems—Tenth Revision, Canada

‡ PPV = positive predictive value

§ Sensitivity and positive predictive value are only for codes I61, I630, I631, I632, I633, I634, I635, I638, I639, and I64

‖ Sensitivity and positive predictive value are only for code I21

**RPDB = Registered Persons Database

†† Sensitivity and positive predictive value only for code J18

LOS = length of stay

Appendix C: Length of stay (days) distributions by procedure type comparing combined anesthesia (general and neuraxial) with general anesthesia

Procedure Name	Anesthesia Type	Percentile					*P* value
		10th	25th	50th	75th	90th	
Abdominal aorta repair using open approach with synthetic material (e.g., Teflon felt, Dacron, Nylon, Orlon).	General	2	3	5	7	9	0.113
	Combined	3	4	5	7	9	
Abdominal aorta bypass using synthetic material; bypass terminating at lower limb vessels (e.g., iliac, femoral, popliteal, tibial).	General	4	5	7	8	11	0.807
	Combined	5	6	7	8	9	
Arteries of leg bypass not elsewhere classified using autograft (e.g., saphenous vein); bypass terminating in lower limb artery (e.g., femoropopliteal).	General	4	5	6	7	9	0.727

Appendix C continued

Procedure Name	Anesthesia Type	Percentile					*P* value
		10th	25th	50th	75th	90th	
Combined	4	5	6	7	9		
Radical bladder excision with creation of continent urinary reservoir and permanent cutaneous stoma.	General	2	4	6	8	12	0.021
	Combined	5	5	7	9	12	
Radical bladder excision using open approach.	General	2	3	4	5	8	0.001
	Combined	3	4	5	7	9	
Partial large intestine excision using open approach; enterocolostomy anastomosis technique.	General	4	5	6	8	10	0.335
	Combined	3	4	6	7	10	
Partial large intestine excision using open approach; colocolostomy anastomosis technique.	General	3	4	5	7	11	0.206
	Combined	4	5	5	7	8	
Partial large intestine excision open approach; colorectal anastomosis technique.	General	2	3	5	7	10	0.510
	Combined	2	4	5	7	8	
Reattachment of the large intestine; open approach of colostomy (may involve: reanastomosis of colon to [Hartmann] rectal stump or mucous fistula).	General	4	5	6	8	10	0.003
	Combined	5	6	7	8	10	
Partial large intestine excision using endoscopic (laparoscopic, laparoscopic-assisted, hand-assisted) approach; enterocolostomy anastomosis technique.	General	3	3	4	6	7	0.002
	Combined	3	4	5	6	7	
Small intestine bypass with exteriorization using open approach; end enterostomy (e.g., terminal, end, or loop ileostomy).	General	3	4	4	6	8	<0.001
	Combined	3	4	5	6	8	
Partial large intestine excision using endoscopic (laparoscopic, laparoscopic-assisted, hand-assisted) approach; colocolostomy anastomosis technique.	General	4	5	7	8	11	0.611
	Combined	5	5	7	8	10	
Partial large intestine excision using open approach; stoma formation with distal closure.	General	6	7	8	10	12	0.078
	Combined	7	7	9	10	13	
Total lobe of lung excision using open thoracic approach.	General	4	5	6.5	8	12	0.089
	Combined	5	6	7	8	12	
Partial lobe of lung excision using open thoracic approach.	General	6	7	8	10	13	0.189
	Combined	6	6	8	9	11	
Partial lung excision not elsewhere classified using open thoracic approach.	General	3	5	8	10	12	0.238
	Combined	5	7	8	9	12	
Abdominal cavity release using open approach using device not elsewhere classified.	General	4	5	6	8	10	<0.001
	Combined	5	6	7	8	10	
Partial liver excision using open approach.	General	4	5	7	8	10	0.012
	Combined	5	6	7	8	10	
Partial abdominal cavity excision using open approach.	General	4	6	8	10	13	0.183
	Combined	5	7	8	10	13	
Partial stomach excision without vagotomy using open approach; gastrojejunal (or gastroenteral NEC) anastomosis.	General	6	7	9	11	14	0.279
	Combined	6	7	8	10	12	
Partial pancreas excision with duodenum without vagotomy using open approach.	General	2	3	4	6	9	0.466
	Combined	2	3	4	6	9	

NEC = not elsewhere classified

Appendix D: *Post hoc* subgroup analysis of the association between anesthesia type and primary composite outcome by baseline cardiovascular risk

Exposure Status	Number of Patients	Events *n*	Events %	Odds Ratio	95% CI
Low cardiovascular risk					
General	2,271	19	0.84%	0.87	0.24 to 3.13
Combined	1,376	15	1.09%		
High cardiovascular risk					
General	5,335	143	2.68%	0.90	0.68 to 1.19
Combined	3,397	89	2.62%		

CI = confidence interval

Appendix E: *Post hoc* subgroup analysis of the association between anesthesia type and primary composite outcome by time period

Exposure Status	Number of Patients	Events *n*	Events %	Odds Ratio	95% CI
2004-2007					
General	3,277	71	2.17%	0.92	0.62 to 1.38
Combined	1,976	41	2.07%		
2008-2011					
General	4,329	91	2.10%	1.00	0.72 to 1.38
Combined	2,797	63	2.25%		

CI = confidence interval

References

1. *Ballantyne JC, Carr DB, deFerranti S, et al.* The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998; 86: 598-612.
2. *Block BM*, *Liu SS*, *Rowlingson AJ*, *Cowan AR*, *Cowan JA Jr*, *Wu CL*. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 2003; 290: 2455-63.
3. *Jorgensen H, Wetterslev J, Moiniche S, Dahl JB*. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrance Database Syst Rev 2000; 4: CD001893.
4. *Popping DM*, *Elia N*, *Marret E*, *Remy C*, *Tramer MR*. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg 2008; 143: 990-9.
5. *Rodgers A*, *Walker N*, *Schug S*, *et al*. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321: 1493.
6. *Weetman C*, *Allison W*. Use of epidural analgesia in post-operative pain management. Nurs Stand 2006; 20: 54-64.
7. *Wijeysundera DN*, *Beattie WS*, *Austin PC*, *Hux JE*, *Laupacis A*. Epidural anaesthesia and survival after intermediate-to-high risk non-cardiac surgery: a population-based cohort study. Lancet 2008; 372: 562-9.
8. *Beattie WS*, *Badner NH*, *Choi P*. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg 2001; 93: 853-8.
9. *Bignami E*, *Landoni G*, *Biondi-Zoccai GG*, *et al*. Epidural analgesia improves outcome in cardiac surgery: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 2010; 24: 586-97.
10. *Leslie K*, *Myles P*, *Devereaux P*, *et al*. Neuraxial block, death and serious cardiovascular morbidity in the POISE trial. Br J Anaesth 2013; 111: 382-90.
11. *von Elm E*, *Altman DG*, *Egger M*, *Pocock SJ*, *Gotzsche PC*, *Vandenbroucke JP*; *STROBE Initiative*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008; 61: 344-9.
12. *Molnar AO*, *Coca SG*, *Devereaux PJ*, *et al*. Statin use associates with a lower incidence of acute kidney injury after major elective surgery. J Am Soc Nephrol 2011; 22: 939-46.
13. *Siddiqui NF*, *Coca SG*, *Devereaux PJ*, *et al*. Secular trends in acute dialysis after elective major surgery—1995 to 2009. CMAJ 2012; 184: 1237-45.
14. *Vinden C*, *Nash DM*, *Rangrej J*, *et al*. Complications of daytime elective laparoscopic cholecystectomies performed by surgeons who operated the night before. JAMA 2013; 310: 1837-41.
15. *Hwang YJ*, *Shariff SZ*, *Gandhi S*, *et al*. Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. BMJ Open 2012; DOI:10.1136/bmjopen-2012-001821.
16. *Juurlink DN, Preyra C, Croxford R, et al.* Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto, ON. ICE Investigative Report, 2006. Available from URL: http://www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information (accessed November 2014).
17. *Montori VM*, *Permanyer-Miralda G*, *Ferreira-Gonzalez I*, *et al*. Validity of composite end points in clinical trials. BMJ 2005; 330: 594-6.
18. *Pogue J*, *Devereaux PJ*, *Thabane L*, *Yusuf S*. Designing and analyzing clinical trials with composite outcomes: consideration of possible treatment differences between the individual outcomes. PLoS One 2012; 7: e34785.
19. *American Heart Association.* Heart Attack Risk Assessment - 2012. Available from URL: http://www.heart.org/HEARTORG/Conditions/HeartAttack/HeartAttackToolsResources/Heart-Attack-Risk-Assessment_UCM_303944_Article.jsp (accessed November 2014).
20. *Austin PC*. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Communications in Statistics - Simulation and Computation 2009; 38: 1228-34.
21. *Austin PC*. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011; 46: 399-424.
22. *Ury HK*. Efficiency of case-control studies with multiple controls per case: continuous or dichotomous data. Biometrics 1975; 31: 643-9.

23. *Yeager MP*, *Glass DD*, *Neff RK*, *Brinck-Johnsen T*. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 1987; 66: 729-36.
24. *Gulur P*, *Nishimori M*, *Ballantyne JC*. Regional anaesthesia versus general anaesthesia, morbidity and mortality. Best Pract Res Clin Anaesthesiol 2006; 20: 249-63.
25. *Hong JY*, *Lee SJ*, *Rha KH*, *Roh GU*, *Kwon SY*, *Kil HK*. Effects of thoracic epidural analgesia combined with general anesthesia on intraoperative ventilation/oxygenation and postoperative pulmonary complications in robot-assisted laparoscopic radical prostatectomy. J Endourol 2009; 23: 1843-9.
26. *Le-Wendling L*, *Bihorac A*, *Baslanti TO*, *et al*. Regional anesthesia as compared with general anesthesia for surgery in geriatric patients with hip fracture: does it decrease morbidity, mortality, and health care costs? Results of a single-centered study. Pain Med 2012; 13: 948-56.
27. *Jha P*, *Deboer D*, *Sykora K*, *Naylor CD*. Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population-based comparison. J Am Coll Cardiol 1996; 27: 1335-42.
28. *Canadian Institute for Health Information.* Data Quality of the Discharge Abstract Database Following the First-Year Implementation of ICD-10-CA/CCI Final Report. Ottawa, ON, September 2004. Available from URL: https://secure.cihi.ca/estore/productSeries.htm?locale=en&pc=PCC228 (accessed November 2014).