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

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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.

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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.*

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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 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

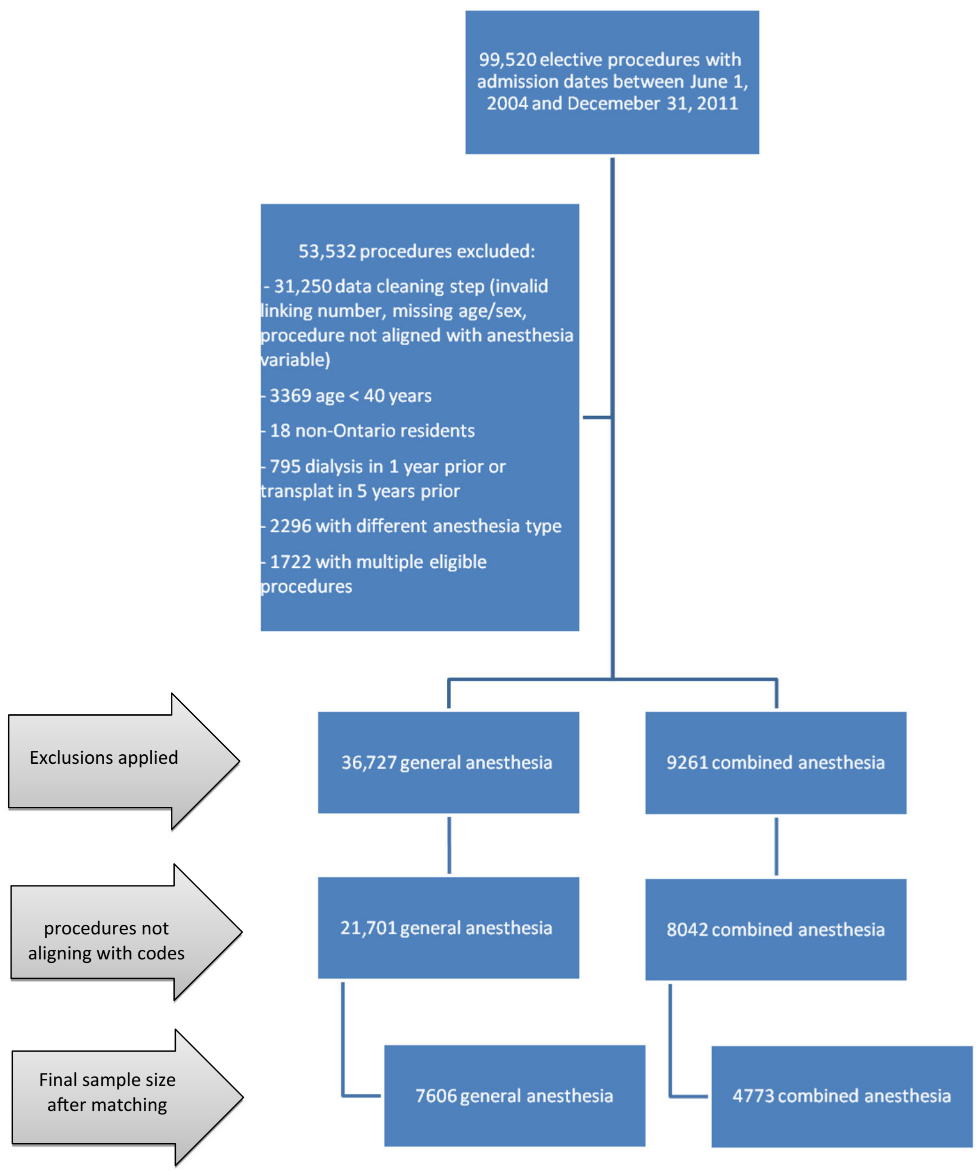

Figure Participant flow diagram

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 $mL{\cdot}min^{-1}$ 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 $mL{\cdot}min^{-1}$ 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]‡

Appendix B continued

Outcome	Databases	Codes	Validity
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	

Appendix C continued

Procedure Name	Anesthesia Type	Percentile					P value
		10th	25th	50th	75th	90th	
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

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