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Clinical Practice

Covert stroke after non-cardiac surgery: a prospective cohort study

M. Mrkobrada[1,*], M. D. Hill[2], M. T. V. Chan[3], A. Sigamani[4], D. Cowan[5], A. Kurz[6], D. I. Sessler[6], M. Jacka[7], M. Graham[7], M. Dasgupta[1], V. Dunlop[8], D. J. Emery[7], I. Gulka[9], G. Guyatt[5], D. Heels-Ansdell[5], J. Murkin[1], S. Pettit[8], D. J. Sahlas[5], M. Sharma[5], M. Sharma[1], S. Srinathan[10], P. St John[10], S. Tsai[11], A. W. Gelb[12], M. O'Donnell[5], D. Siu[3], P. W. Y. Chiu[3], V. Sharath[4], A. George[4] and P. J. Devereaux[5]

[1]University of Western Ontario, 339 Windermere Road B9-100, London, ON, Canada N6A 5A5, [2]University of Calgary, Calgary, AB, Canada, [3]Chinese University of Hong Kong, Hong Kong, SAR, China, [4]St John's Medical College and St John's Research Institute, Bangalore, India, [5]McMaster University, Hamilton, ON, Canada, [6]Cleveland Clinic, Cleveland, OH, USA, [7]University of Alberta Hospital, Edmonton, AB, Canada, [8]Population Health Research Institute, Hamilton, ON, Canada, [9]London Health Sciences, London, ON, Canada, [10]University of Manitoba, Winnipeg, MB, Canada, [11]Hamilton Health Sciences, Hamilton, ON, Canada, and [12]University of California, San Francisco, CA, USA

*Corresponding author. E-mail: mmrkobr@uwo.ca

Abstract

Background: Overt stroke after non-cardiac surgery has a substantial impact on the duration and quality of life. Covert stroke in the non-surgical setting is much more common than overt stroke and is associated with an increased risk of cognitive decline and dementia. Little is known about covert stroke after non-cardiac, non-carotid artery surgery.

Methods: We undertook a prospective, international cohort study to determine the incidence of covert stroke after non-cardiac, non-carotid artery surgery. Eligible patients were ≥65 yr of age and were admitted to hospital for at least three nights after non-cardiac, non-carotid artery surgery. Patients underwent a brain magnetic resonance study between postoperative days 3 and 10. The main outcome was the incidence of perioperative covert stroke.

Results: We enrolled a total of 100 patients from six centres in four countries. The incidence of perioperative covert stroke was 10.0% (10/100 patients, 95% confidence interval 5.5–17.4%). Five of the six centres that enrolled patients reported an incident covert stroke, and covert stroke was found in patients undergoing major general (3/27), major orthopaedic (3/41), major urological or gynaecological (3/22), and low-risk surgery (1/12).

Conclusions: This international multicentre study suggests that 1 in 10 patients ≥65 yr of age experiences a perioperative covert stroke. A larger study is required to determine the impact of perioperative covert stroke on patient-important outcomes.

Clinical trial registration: NCT01369537.

Key words: magnetic resonance imaging; perioperative period; stroke

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Editor's key points

- In non-surgical settings, covert strokes are associated with cognitive and functional decline.
- The authors determined the incidence of covert strokes in elderly patients undergoing non-cardiac, non-carotid surgery.
- Magnetic resonance imaging revealed a covert stroke incidence of 10%.

Non-cardiac surgery provides substantial benefit to patients but is associated with an increased risk of major vascular complications, including stroke. The estimates of the risk of perioperative stroke in the current literature range between 0.2 and 4.3%.[1–5] Although only a small proportion of patients suffer a perioperative clinically overt stroke, these strokes often have a devastating effect on patients' quality and duration of life.[1]

The POISE Trial included 8351 adults from 123 centres in 23 countries undergoing non-cardiac surgery.[1] The incidence of overt stroke was 0.7% and was associated with a high burden of mortality (32% of patients died after a postoperative stroke) and morbidity (59% of the patients with non-fatal stroke required help to perform everyday activities or were incapacitated at the 30 day follow-up).

In contrast, covert stroke is an acute cerebral ischaemic event that is not clinically apparent. In the non-operative setting, covert stroke is associated with cognitive decline, motor impairment, dependence, and death.[6 7] Modern neuroimaging techniques can detect acute covert stroke with high sensitivity.[7 8] Although a number of large studies have shown a high prevalence of covert stroke in the general population of older adults,[9 10] only a few small studies have evaluated the frequency of covert stroke in the perioperative setting, and these studies were confined to cardiac[11–18] and carotid artery surgical[19] populations. No studies have examined the incidence of covert stroke after non-cardiac surgery that does not directly manipulate the arterial blood supply to the brain.

Methods

This study was a multicentre prospective cohort study of patients undergoing non-cardiac surgery. Our primary objectives were as follows: (i) to develop a preliminary estimate of the incidence of postoperative covert stroke; and (ii) to determine the feasibility of a full, definitive study of the incidence, determinants, and consequences of perioperative covert stroke. We recruited patients from centres in Canada, China, India, and the USA. The research ethics board at each site approved the protocol before patient recruitment.

The protocol was registered with ClinicalTrials.gov (identifier NCT01369537) and was approved by the Research Ethics Board at McMaster University (project number 11-211).

Eligibility criteria

Patients ≥65 yr of age undergoing non-cardiac surgery who required hospital admission were eligible for the study. We excluded patients who underwent carotid artery surgery, had a contraindication to a magnetic resonance (MR) imaging study (e.g. implanted devices not safe for MR studies, or severe claustrophobia), were unable to complete a telephone interview, had a previously documented history of dementia, or resided in a nursing home. We also excluded patients who did not receive neuraxial or general anaesthesia or did not require a hospital stay of ≥3 days.

Patient recruitment

We developed a recruitment schedule that ensured proportionate representation of patients in the study that reflected the worldwide surgical population, as documented in the VISION Study, a 40 000-patient international prospective cohort study of unselected adult patients undergoing non-cardiac surgery requiring hospital admission.[20] Patients were considered enrolled in the study once the MR study was completed in the postoperative period.

Data collection

Research staff obtained patient consent and collected baseline assessments before the day of surgery. Baseline clinical variables included the type of surgery (see Appendix), vascular risk factors and co-morbidities, a cognitive screen using the Montreal Cognitive Assessment (MoCA) instrument,[21] functional assessments using the modified Rankin score[22] and Lawton instrumental activities of daily living (iADL) questionnaire,[23] and quality of life as measured by the EuroQol five dimensions questionnaire.[24] All research staff were trained in the administration of the Confusion Assessment Method (CAM) by a geriatrician. According to study protocol, the research staff assessed patients in the morning and the afternoon to collect data on clinical outcomes and the presence of delirium using the CAM.[25] Research staff contacted patients by telephone 30 days after the surgery to collect data regarding clinical outcomes, physical function, and quality of life.

Magnetic resonance study protocol

Standardized MR imaging of the brain was performed between postoperative days 3 and 10, as soon as the patient was able to tolerate this procedure. The MR study sequences included axial fluid attenuated inversion recovery, gradient echo, T2, and diffusion-weighted imaging (DWI). The MR sequences were performed according to the local standard of care with a minimal 1.5 T MR machine and a slice thickness of 3–5 mm, with no gap. The DWI sequence enabled the detection of acute covert stroke that had occurred within 10 days of the study.[8 26] Diffusion restriction, manifested as hyperintensity on DWI sequences with corresponding lesion on the apparent diffusion coefficient map, suggest acute ischaemia. These findings are attributable to the failure of energy-dependent membrane ion pumps and the development of cytotoxic oedema, which is the characteristic neuroimaging finding of acute ischaemia. Diffusion-weighted imaging lesions attributable to non-ischaemic causes are rare and distinguished by the pattern on magnetic resonance images (MRIs).

The MR imaging results were not blinded to the patients, attending physicians, radiologists, or the study team.

Patient identifiers were removed, and MR images were electronically transferred via a secure encrypted connection to the central imaging interpretation centre. A neurologist and neuroradiologist who were blinded to the baseline characteristics and clinical outcomes independently assessed the MR studies in duplicate and provided a consensus interpretation regarding the presence of imaging lesions that represent acute perioperative cerebral ischaemia and chronic ischaemic findings, defined according to recent consensus criteria.[27] Any disagreements were resolved by consensus.

Table 1 Preoperative participant characteristics and type of surgery. EQ-5D, EuroQol five dimensions questionnaire; IQR, interquartile range; Lawton iADL, Lawton instrumental activities of daily living; MoCA, Montreal Cognitive Assessment. *Some patients underwent multiple surgical interventions during their index surgery; therefore, the total number does not add up to 100

Patient characteristics and type of surgery	All patients (*n*=100)	No covert stroke (*n*=90)	Covert stroke (*n*=10)
Age [yr; *n* (%)]			
65–74	57 (57)	53 (59)	4 (40)
≥75	43 (43)	37 (41)	6 (60)
Females [*n* (%)]	47 (47)	42 (47)	5 (50)
Risk factors [*n* (%)]			
History of coronary artery disease	18 (18)	16 (18)	2 (20)
History of stroke	5 (5)	4 (4)	1 (10)
History of a transient ischaemic attack	4 (4)	3 (3)	1 (10)
Diabetes	21 (21)	20 (22)	1 (10)
Hypertension	71 (71)	66 (73)	5 (50)
Current atrial fibrillation	4 (4)	4 (4)	0 (0)
Obstructive sleep apnoea	8 (8)	8 (9)	0 (0)
Chronic obstructive pulmonary disease	11 (11)	11 (12)	0 (0)
Type of surgery [*n* (%)]*			
Major vascular	1 (1)	1 (1)	0 (0)
Major general	27 (27)	24 (27)	3 (30)
Major thoracic	1 (1)	1 (1)	0 (0)
Major urological or gynaecological	22 (22)	19 (21)	3 (30)
Major orthopaedic	41 (41)	38 (42)	3 (30)
Major neurosurgery	1 (1)	1 (1)	0 (0)
Low risk	12 (12)	11 (12)	1 (10)
Chronic neuroimaging findings			
Old ischaemic lesions	33 (33%)	29 (32%)	4 (40%)
Leucoaraiosis	64 (64%)	58 (64%)	6 (60%)
Preoperative assessments			
MoCA [mean (SD)]	22.30 (4.94)	22.26 (4.97)	22.60 (5.02)
EQ-5D [mean (SD)]	0.77 (0.19)	0.77 (0.19)	0.76 (0.26)
Lawton iADL [median (IQR)]	8 (7–8)	8 (7–8)	7.5 (7–8)
Modified Rankin score [median (IQR)]	0.5 (0–2)	1 (0–2)	0 (0–1)

Statistical analysis

The sample size for this pilot study is a convenience sample to demonstrate feasibility. We determined the clinical characteristics at baseline in the entire study population and separately for patients who did and did not suffer a covert stroke. We reported the incidence of acute covert stroke in the study population and the 95% confidence intervals (CIs). We also reported the incidence of acute overt stroke, diagnosed before the MR scan, overt stroke diagnosed within 24 h after the MR scan, and overt stroke diagnosed >24 h after the MR scan. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Table 2 Covert stroke result at each centre

Acute covert stroke	Total (*n*=100)
All centres	10 (10%) 95% CI (6–17%)
Hamilton, ON, Canada	3/25 (12%)
Edmonton, AB, Canada	0/5 (0%)
London, ON, Canada	2/25 (8%)
Hong Kong, China	2/20 (10%)
Bangalore, India	2/20 (10%)
Cleveland, OH, USA	1/5 (20%)

Results

From September 2011 until December 2012, we enrolled 100 patients from six centres in four countries; all patients completed the 30 day follow-up.

Table 1 reports the preoperative characteristics. Forty-three per cent of enrolled patients were ≥75 yr of age and 47% of patients were women. The most common cardiovascular risk factors were hypertension (71 patients), diabetes (21 patients), and a history of coronary artery disease (18 patients). Five patients had a history of stroke, four patients had a history of a transient ischaemic attack, and four patients were in atrial fibrillation before surgery. The most common surgeries were major orthopaedic (41 patients), major general (27 patients), and urological or gynaecological (22 patients).

All patients had an MR study of the brain between postoperative days 3 and 10 (median postoperative day 4, interquartile range 3–5.25 days after surgery). There was a high prevalence of chronic ischaemic lesions (reported in 33% of the overall population) and ischaemic leucoaraiosis (reported in 64% of the overall population).

The incidence of covert stroke was 10.0% (10/100 patients; 95% CI, 5.5–17.4%). The chance-corrected agreement between MRI interpreters for the presence of acute ischaemic lesions was very good (κ=0.94). Five of the six centres reported at least one covert stroke (Table 2). Covert stroke occurred 3 of 41 patients (7.3%) who

Table 3 Clinical outcomes. PACU, postanaesthesia care unit. *n=99 (one patient went directly from OR to ICU), n=90 for no covert stroke, n=9 for covert stroke; †n=99 (n=89 for no covert stroke, n=10 for covert stroke) because delirium assessments were not performed on one patient

Clinical outcome	All patients (n=100)	No covert stroke (n=90)	Covert stroke (n=10)
Delirium within first 3 days after surgery [n (%)]†	8 (8)	7 (8)	1 (10)
Death during first 30 days after surgery [n (%)]	0 (0)	0 (0)	0 (0)
Elevated troponin marker during first 30 days after surgery [n (%)]	17 (17)	15 (17)	2 (20)
Hypotension			
<90 mm Hg intraoperative	36 (36)	32 (36)	4 (40)
<90 mm Hg in PACU*	7 (7)	7 (8)	0 (0)
<90 mm Hg post-PACU to discharge	21 (21)	17 (19)	4 (40)

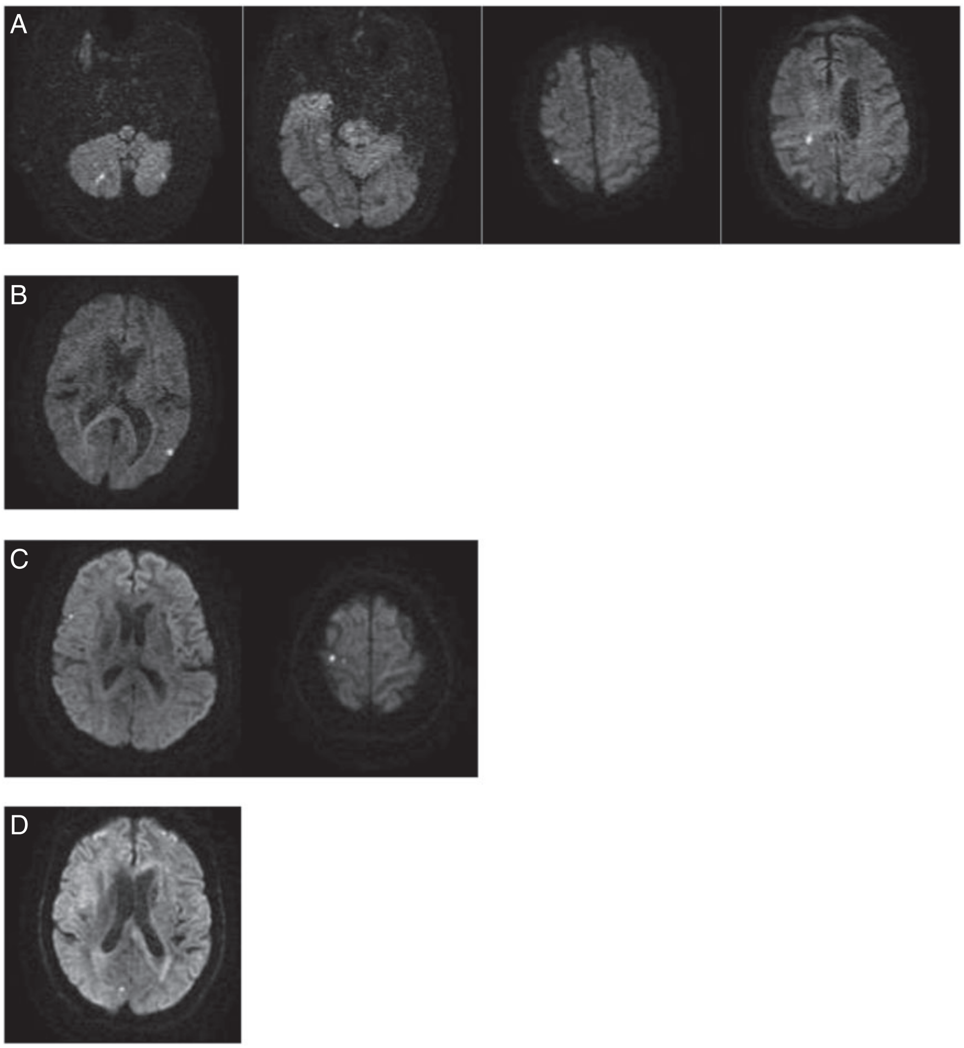

Fig 1 Examples of acute ischaemic lesions in study participants, as demonstrated on diffusion-weighted imaging sequences. (A) A patient with multiple acute ischaemic lesions in the cerebellum, parietal lobe, and corona radiata. (B) A patient with a single acute ischaemic lesion in the temporal cortex. (C) A patient with multiple acute ischaemic lesions in the right frontal lobe. (D) A patient with a single acute ischaemic lesion in the right occipital lobe.

underwent major orthopaedic, 3 of 27 patients (11%) who underwent major general, 3 of 22 patients (14%) who underwent major urological or gynaecological surgery, and 1 of 12 patients (8%) who underwent low-risk surgery. Table 3 reports the clinical outcomes, and examples of representative MRIs demonstrating acute cerebral ischaemic lesions are shown in Fig. 1.

A single overt stroke was clinically diagnosed only after the research MR study of the brain demonstrated findings of acute ischaemia on postoperative day 6. In this patient who underwent a liver resection, the routine daily clinical assessments did not document the presence of a neurological deficit, and we documented this as a covert stroke as per research protocol. However, a neurology consultation was requested because of the findings on the research MR study. The detailed neurological clinical assessment documented a substantial right-sided ataxia that was in keeping with the imaging findings.

Eight patients in the overall study population (1/10 patients with covert stroke) developed delirium during the first 3 days after surgery. No patients died in the 30 day postoperative follow-up. Routine cardiac troponin concentrations were measured as a part of the standard of care, and 17 patients out of 100 (2/10 patients with covert stroke) had an elevated troponin measurement after surgery.

Discussion

This study demonstrated a 10% incidence of covert stroke after non-cardiac surgery. Covert stoke was documented in patients across a broad group of non-cardiac surgeries (i.e. orthopaedic, general, urological or gynaecological, and low-risk surgeries).

One patient who had experienced an overt stroke was diagnosed as a result of the research MR study; after the MR study that demonstrated acute ischaemic lesions, the patient was found to have previously unappreciated neurological deficits. This incident demonstrates how neurological symptoms attributable to stroke may be missed in the postoperative period because of the effects of postoperative pain, medication, and limited mobility, suggesting the possibility that some postoperative strokes are not being diagnosed. The study protocol did not mandate a neurological examination in all patients with acute perioperative covert strokes, and we cannot exclude the possibility that other patients with covert infarcts had clinical manifestations that were not detected in the process of routine postoperative care.

We found a high prevalence of chronic ischaemic findings on MR imaging and a high prevalence of a history vascular disease and of risk factors for vascular disease. The high burden of medical co-morbidity in the study population is in keeping with the findings of the VISION Study, a recently published large prospective cohort study of a representative sample of adults undergoing non-cardiac surgery.[20]

This is the first study of covert stroke after non-cardiac, noncarotid artery surgery and one of the largest studies of postoperative covert stroke. We demonstrated a similar incidence of perioperative covert stroke as has been documented in studies of patients undergoing carotid endarterectomy (pooled estimate 10%), and this is also in the range of what has been documented after cardiac surgery (range 16–45%).[11–18] Patients in this study were recruited from a broad range of surgical disciplines, and the surgical distribution was similar to that of worldwide patients undergoing non-cardiac, non-carotid artery surgery.[20] We also demonstrated the feasibility of the study protocol with an excellent recruitment rate, good protocol adherence, and no loss to follow-up.

The major limitation of this study is that it was not powered to inform the clinical and the cognitive impact of covert stroke. Covert cerebral ischaemia in the non-surgical setting is associated with an increased risk of cognitive impairment, overt stroke, and death,[28] but the impact of perioperative covert stroke has not been studied. Patients with perioperative covert stroke may suffer a decline in physical function, quality of life, and cognitive function. Given the large volume of surgery worldwide, covert perioperative stroke may therefore represent a substantial population risk factor for development of cognitive impairment.[29]

This study may have suffered from selection bias, because only patients who were able to undergo an MRI between postoperative days 3 and 9 were included. However, as the first ever study of covert brain ischaemia in this population, we did demonstrate a high incidence of covert stroke and good feasibility of the study protocol. Future studies will need to determine the long-term impact of covert stroke after non-cardiac surgery.

Conclusion

This study suggests there is a substantial risk of covert stroke after non-cardiac surgery. Given that globally 200 million adults undergo major non-cardiac surgery every year, postoperative covert stroke may be responsible for a substantial proportion of small vessel cerebral ischaemic disease in the overall population. A larger study is needed to determine the impact of postoperative covert stroke on patient-important outcomes.

Authors' contributions

All authors contributed to the study design and the analysis and interpretation of data. All authors were involved in drafting of the manuscript and approved the final version for publication. M.M. has full access to all study data and takes responsibility for data integrity and the accuracy of the data analysis.

Declaration of interest

M.D.H. is an employee of the University of Calgary. The University of Calgary has received unrestricted grants from Covidien (Medtronic) and from Hoffmann-La Roche Canada for the conduct of clinical trials in stroke. M.D.H. is a current consultant to Merck as an adjudicator for adverse events for a series of clinical trials sponsored by Merck, and has ownership of stock in Calgary Scientific Incorporated. P.J.D. reports grants from Canadian Institutes for Health Research, during the conduct of the study; grants from Abbott Diagnostics, grants from AstraZeneca, grants from Bayer, grants from Boehringer Ingelheim, grants from Bristol-Myers Squibb, grants from Covidien, grants from Roche Diagnostics, and grants from Styker. P.St J. reports that he sits on the Winnipeg Regional Health Authority Rehab and Geriatrics Programme council and is co-Chair of the Winnipeg Regional Health Authority Geriatric and Longterm Care formulary, for which he receives remuneration. M.T.V.C. sits on the *BJA* editorial board. All of the other authors report no conflict of interest. The study funders have no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation.

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Appendix: Surgical definitions

Vascular surgery

Thoracic aorta reconstructive vascular surgeries and above knee amputation (thoracic aorta aneurysm repair, repair of supra-aortic trunks not requiring total cardiopulmonary bypass, thoraco-abdominal aortic aneurysm repair with or without aorto-femoral bypass, above knee amputation)

Aorto-iliac reconstructive vascular surgery (open abdominal aortic aneurysm repair, aortofemoral bypass, iliac-femoral bypass, renal artery revascularization, celiac artery revascularization, superior mesenteric artery revascularization)

Peripheral vascular reconstruction without aortic cross-clamping (axillo-femoral bypass, femoral-femoral bypass, femoro-infragenicular bypass, profundoplasty or other angioplasties of the infrainguinal arteries)

Endovascular abdominal aortic aneurysm repair

Lower leg amputation (amputation below knee but above foot)

General Surgery

Complex visceral resection (surgery involving the liver, esophagus, pancreas or multiple organs)

Partial or total colectomy or stomach surgery

Other intra-abdominal surgery (gallbladder, appendix, adrenals, spleen, lymph node dissection)

Major head and neck resection for tumor

Thoracic Surgery

Pneumonectomy

Lobectomy

Other thoracic (wedge resection of lung, resection of mediastinal tumor, major chest wall resection)

Major Orthopedic Surgery

Major hip or pelvis surgery (hemi or total hip arthroplasty, internal fixation of hip, pelvic arthroplasty)
Internal fixation of femur
Knee arthroplasty

Major Urology or Gynecology Surgery

Visceral resection (i.e., nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration [i.e., radical procedure for cancer to remove pelvic organs])
Cytoreduction surgery
Radical hysterectomy
Hysterectomy
Radical prostatectomy
Transurethral prostatectomy

Low-Risk Surgeries

Parathyroid, thyroid, breast, hernia, local anorectal procedure, oophorectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmology, ears/nose/throat surgery, vertebral disc surgery, spinal fusion, hand surgery, cosmetic surgery, arterio-venous access surgery for dialysis, other surgeries

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