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Multiple sclerosis relapse risk in the postoperative period: effects of invasive surgery and anesthesia

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Abstract

Background: Postoperative multiple sclerosis (MS) relapses are a concern among patients and providers.

Objective: To determine whether MS relapse risk is higher postoperatively.

Methods: Data were extracted from medical records of MS patients undergoing surgery at a tertiary center (2000–2016). Conditional logistic regression estimated within-patient unadjusted and age-adjusted odds of postoperative versus preoperative relapse.

Results—Among 281 patients and 609 surgeries, 12 postoperative relapses were identified. The odds of postoperative versus preoperative relapse in unadjusted (OR=0.56, 95% CI:0.18–1.79; P=0.33) or age-adjusted models (OR=0.66, 95% CI:0.20–2.16; P=0.49) were not increased.

Conclusions: Surgery/anesthesia exposure did not increase postoperative relapse risk. These findings require confirmation in larger studies.

Keywords

anesthesia; preoperative period; postoperative period; logistic models; multiple sclerosis; retrospective studies

INTRODUCTION

Risk of postoperative relapse is a common concern among patients with multiple sclerosis (MS) and their health providers, including neurologists, anesthesiologists, and surgeons. The perception that MS patients are at an increased risk of relapse following anesthesia

administration and surgery can impact clinical decision making, resulting in delays of necessary surgery and neurology consultation for preoperative clearance. However, evidence that surgery or anesthesia can precipitate relapses is limited to case series.^{1–3} To our knowledge, no prior studies have systematically investigated the role of surgery or anesthesia administration on relapse risk.

The objective of this study was to determine the postoperative relapse risk in MS patients undergoing an invasive surgical procedure requiring anesthesia. We hypothesized that, in the absence of infection or postoperative complications that could trigger functional decline or symptom recrudescence, postoperative relapse risk would not significantly differ from preoperative relapse risk.

METHODS

We performed a retrospective chart review of patients 18 years or older continuously followed in the University of Michigan (U-M) MS clinic (1/1/00–7/1/16). This study was approved by the U-M Institutional Review Board. Informed consent was not required. MS diagnosis was confirmed by investigators based on review of clinical documentation from U-M MS specialists. Patients who underwent an invasive surgical procedure requiring anesthesia (excluding minimal sedation, regional, topical, or local anesthesia) were identified using a web-based search engine that searches medical charts in the U-M Clinical Data Repository for specific diagnostic or procedural codes, keywords or phrases.⁴ All surgeries were performed at U-M Hospital. Given the potential overlapping effects on function and potency of concomitant treatments (immunosuppressive therapy/radiation), patients with active malignancy (except non-metastatic prostate cancer), sarcoidosis, collagen vascular disease, Lyme disease, syphilis, concomitant neurologic disease, or human immunodeficiency virus were excluded. Surgical procedures requiring minimal/no sedation, procedures expected to alter postoperative neurologic examinations (e.g. baclofen pump procedures), and procedures associated with immunosuppressive therapy use that may affect MS relapse rate (e.g. organ transplants) were also excluded.

Demographic and clinical variables extracted from medical charts included age, sex, race/ethnicity, smoking status, MS subtype (relapsing/progressive), disease modifying therapy prior to surgery (yes/no), enhancing lesions on the most recent pre-procedure brain or spinal cord MRI (yes/no), pre- and postoperative relapse dates, and surgical procedure type. Given typical variations in anesthesia modality by surgical procedure, procedures were further characterized as minor and major (supplemental Table 1). Relapses were defined as the presence of an acute, objective, neurological change lasting 24 hours or longer, in the absence of a concurrent documented infection or fever. All potential relapses were reviewed (n=14) by two board certified neurologists (TJB, LBD).

Relapse status was obtained for two years prior and 90 days following each surgical event. A 90 day post-operative window was selected based on prior studies of relapses that followed other monophasic, physiologically stressful events.^{5, 6} Data were organized as a series of relapse status indicators for each patient on each day, and a series of exposure indicators signaling whether a patient was within a 90-day postoperative period. For patients with

multiple surgeries where the pre- and postoperative periods could overlap, relapses were considered postoperative. To minimize dependence between events, we excluded 14 days of data following a relapse in the preoperative period and the remainder of any postoperative period following a relapse.

Discrete time survival analysis using conditional logistic regression was used to regress the outcome (relapse) on an exposure (surgical procedure) and other control variables. The exposure indicator in the regression was zero when a patient was in a preoperative period and declined linearly from one to zero over the 90-day postoperative period. The regression coefficient for the exposure indicator is the log odds for the association between surgical procedure and relapse risk. Conditional logistic regression accounts for within-patient clustering, controls for fixed between-patient heterogeneity (including disease modifying therapy use, sex, race, smoking, MS subtype and presence of enhancing lesions on pre-procedure MRI), and addresses rare events of interest. As a time-varying confounder, age was additionally included in an adjusted model. Postoperative relapse risk was estimated for all surgical procedures and within a sample stratified by minor or major surgical procedure (supplemental Table 1).

Statistical analyses were performed using R (version 3.4.2) statistical software.

RESULTS

Among 281 patients and 609 surgeries (n=311 major; n=299 minor), 12 postoperative relapses were identified. None were excluded for infection. The mean age (SD, range) was 49 years (SD 9.9, range:18–75). Most were women, white, non-smokers, with relapsing MS (Table 1). Patients with postoperative relapses were significantly younger and had a higher frequency of enhancing lesions on preoperative MRI. Patient characteristics by procedure are in supplemental Table 2.

The crude estimate of the pre- and postoperative annualized relapse rates were 7.1% and 5.5% per patient per year, respectively. The odds of a postoperative relapse did not significantly differ from the odds of a preoperative relapse even after adjusting for age and all other fixed between patient variables (Table 2).

DISCUSSION

This retrospective study of adults with MS suggests that the risk of relapse is not increased by exposure to invasive surgical procedures requiring anesthesia. To our knowledge, this is the first systematic study of postoperative relapse risk in MS patients, providing new data to guide medical decision making.

Prior data guiding perioperative risk stratification of MS patients is limited. Case series collectively reporting outcomes of 15 patients (20 surgeries) have provided the only evidence of a possible association between surgery or anesthesia and MS relapse. Postoperative neurologic deterioration was noted following ten of the surgeries, with six occurring in the setting of postoperative fever.¹ In the remaining four cases, presence or absence of fever was unreported.² As fever can temporarily worsen MS deficits in the

absence of new lesion formation, we excluded all cases of neurological worsening occurring in the setting of a postoperative infection. A similar approach was employed in a recent obstetrical study of MS patients and found no association between epidural anesthesia or delivery type (vaginal versus cesarean) and MS relapse risk.⁷

Some limitations should be acknowledged. Only those procedures occurring at our institution within a 90-day window were captured. Relapses outside this window or captured at other institutions could have been missed. Our population was also older, which could influence the relapse rate. Descriptive relapse information and perioperative DMT use was not captured, but may be important for future studies. Postoperative relapse events were infrequent; however, conditional logistic regression is designed for analyses of rare events. Lastly, our study is underpowered to find a postoperative risk increase less than two times the preoperative baseline risk.

These findings suggest that MS patients are unlikely to be an increased risk of relapse following surgery requiring anesthesia. Although larger, confirmatory studies are necessary, our data challenge longstanding assumptions regarding postoperative relapse risk for individuals with MS and could inform decision making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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University of Michigan (sponsors include Genzyme-Sanofi and Genentech-Roche). She is also a consultant for Jazz pharmaceuticals.

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Table 1.

Demographic and health characteristics of 281 patients with multiple sclerosis (MS) at enrollment.

	Total sample	No postoperative relapse	Postoperative relapse	<i>p</i> value ^a
Sample size, <i>N</i> (%)	281	269 (96)	12 (4)	
Age, mean (standard deviation)	49 ± 9.9	49 ± 9.8	39 ± 8.8	0.003
Sex				
Women	209	199	10	0.74
Men	72	70	2	
Race/Ethnicity				
Black	36	35	1	1.00
White	239	228	11	
Hispanic or Asian	6	6	0	
Smoking				
No	230	222	8	0.24
Yes	51	47	4	
MS subtype				
Progressive MS	105	103	2	0.22
Relapsing MS	176	166	10	
Disease modifying therapy				
No	138	132	6	1.00
Yes	143	137	6	
Enhancing lesions on MRI ^b				
No	133	130	3	0.003
Yes	35	29	6	

MRI: magnetic resonance imaging.

^a *p* values were obtained from Fisher's exact test, except for *p* value for age (*t* test)^b For 113 MS patients, the lesion data are missing.

Table 2.

Odds ratio^a of a postoperative relapse event in a cohort of 281 multiple sclerosis patients.

Procedure type	Model 1: Unadjusted ^b odds ratio (95% CI)	<i>p</i> value	Model 2: Adjusted ^c odds ratio (95% CI)	<i>p</i> value
Minor surgical procedure	0.40 (0.05–2.96)	0.37	0.55 (0.07–4.10)	0.56
Major surgical procedure	0.69 (0.17–2.81)	0.60	0.74 (0.17–3.19)	0.68
Both	0.56 (0.18–1.79)	0.33	0.66 (0.20–2.16)	0.49

CI: confidence interval.

^aOdds ratios in this study are interpreted as the likelihood that a relapse will occur postoperatively given surgery compared to the likelihood that a relapse occurred preoperatively.

^bConditional logistic regression modeling accounts for fixed baseline variables of study participants in unadjusted and adjusted models.

^cModel 2 is age adjusted.