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# Migraine treatment and the risk of postoperative, pain-related hospital readmissions in migraine patients

**Katharina Platzbecker[1], Fanny P Timm[2], Sait Ashina[1,3,4], Timothy T Houle[2] and Matthias Eikermann[1,5]**

## Abstract

**Background:** Migraine treatment may mitigate migraine and associated pain in the perioperative period.
**Objective:** The aim of the study was to estimate the effect of perioperative acute and prophylactic migraine treatment on the risk of postoperative 30-day hospital readmission with an admitting diagnosis specifying any pain complaints among migraine patients.
**Design:** Electronic health records were analysed for 21,932 adult migraine patients undergoing surgery between 2005 and 2017 at Beth Israel Deaconess Medical Center and Massachusetts General Hospital in Boston, Massachusetts, USA.
**Methods:** Perioperative abortive migraine treatment was defined as guideline-recommended medication (triptan, ergotamine, acetaminophen, nonsteroidal anti-inflammatory drug) prescription after surgery, within 30 days after discharge and prior readmission. Perioperatively continued prophylactic migraine treatment was defined as prescription both prior to surgery and perioperatively for recommended medications (beta-blockers, antidepressants, antiepileptics, onabotulinumtoxin A).
**Results:** Overall, 10,921 (49.8%) patients received a prescription for abortive migraine drugs. Of these, 1.2% and 1.5% of patients with and without such prescription were readmitted for pain, respectively. Patients with abortive treatment had lower odds of pain-related readmission (adjusted odds ratio 0.63 [95% confidence interval 0.49–0.81]). Prophylactic migraine treatment showed no effect on pain-related readmission independently of acute treatment (adjusted odds ratio 0.97 [95% confidence interval 0.72–1.32]).
**Conclusions:** Migraine patients undergoing surgery with a perioperative prescription for abortive migraine drugs were at decreased risk of pain-related hospital readmission.

## Keywords

Triptans, acute and prophylactic treatment, surgery, pain

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## Introduction

Unplanned hospital readmissions after discharge from surgery are frequent and cost-intensive. From 2013 to 2016, readmissions in the USA were as frequent as 4.3% after hip or knee arthroplasty and 13.6% after coronary bypass grafting. Hospital readmissions account for a substantial economic burden on health care systems and serve as performance measurements of clinical care (1). In patients with private or Medicaid insurance coverage, readmission costs were approximately $3000 higher than the expenses for the initial hospital stay (2). With the incentive of enhancing

[1]Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[2]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[3]Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[4]Comprehensive Headache Center, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
[5]Clinic for Anesthesiology and Intensive Care, Essen University Hospital, Essen, Germany

**Corresponding author:**
Matthias Eikermann, Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA.
Email: meikerma@bidmc.harvard.edu

patient safety, lowering costs and improving quality of care, Centers for Medicare and Medicaid initiated campaigns to lower readmission rates. The Hospital Readmission Reduction Program publicly reports institution-specific, risk-standardized readmission rates and penalizes hospitals with higher-than-expected rates by up to 3% of annual inpatient payments (3–5). While overall readmission proportions significantly declined following the initiation of financial sanction policies (6), it continues to be crucial to additionally identify potentially preventable risk factors, as well as protective measures in clinical patient care. This may allow for the improvement of patient care, discharge planning and hospital performance, while preventing the withholding of payment reimbursements.

Migraine is associated with unplanned hospital readmission after surgery (7). In particular, pain complaints have been found to be significant and potentially preventable drivers of unplanned hospital readmission in migraine patients undergoing surgery (8). In the perioperative period, patients are likely exposed to factors precipitating migraine attacks, such as stress, fasting, sleep disruption and dietary changes, which are common examples for previously reported migraine triggers (9,10). Due to an impairment of pain modulation in migraine, nociceptive pathways may be hyperexcitable (11), and migraine patients undergoing surgery have been shown to be susceptible to suffering chronic postoperative pain around the surgical field (8,12).

When aiming to prevent hospital readmissions, optimized discharge procedures, including the reconciliation of the discharge medication regimen and the coordination of follow-up prescriptions, are of high significance (13). Given a likely increased susceptibility to perioperative migraine and pain triggers with a subsequently increased risk of any pain-related hospital readmission, we aimed to estimate the effect of perioperative abortive and prophylactic migraine treatment on hospital readmission within 30 days after discharge among migraine patients undergoing surgery.

We hypothesized that guideline-recommended perioperative abortive migraine treatment is associated with a decreased risk of pain-related 30-day hospital readmission in surgical patients with a history of migraine. Secondarily, we hypothesized seeing an analogous effect for preoperatively established and perioperatively continued prophylactic migraine treatment independently of the acute treatment effect.

## Methods

This was a hospital registry study using electronic patient data on file from two healthcare networks in Boston, Massachusetts, USA: Beth Israel Deaconess Medical Center (BIDMC) and Massachusetts General Hospital, Boston (MGH) or affiliated institutions Mass General Waltham, Waltham, and Mass General/North Shore Center for Outpatient Care, Danvers. The study protocol with a waiver of informed consent was approved by both the Committee on Clinical Investigation at BIDMC (protocol number: 2019P000294) and the Partners Human Research Committee (reliance agreement ID: 1925).

Data were obtained from various clinical databases at both institutions. We used the Anesthesia Information Management System (AIMS), the perioperative Information Management System (PIMS), Casemix, and the "Admission – Discharge – Transfer" (ADT) database at BIDMC. At MGH, we used the Research Patient Data Registry (RPDR), the Enterprise Performance Systems Incorporation (EPSI) database, and the AIMS. All data were combined into a single data repository (Supplement: section 1) (14).

### Study cohort

All adult (age $\geq$18 years) migraine patients who had undergone surgery and survived their index hospital stay were included. Migraine patients were identified based on ICD-9/10 (International Classification of Disease, Ninth/Tenth Revision) diagnostic codes for any diagnosis of migraine with or without aura billed prior to surgery (Supplemental Table 1). Included cases had undergone surgery from 1 October 2005 until 30 September 2017 at BIDMC and from 1 January 2007 until 31 December 2015 at MGH.

Patients with an American Society of Anesthesiologists (ASA) physical status classification of six (brain-dead) were excluded. Further, the final study cohort only included patients with no missing values for all variables considered in the primary analysis. To account for missing data, multiple imputations were performed as part of the sensitivity analyses.

### Definitions

#### Outcome

The outcome was defined as readmission due to any pain complaint within 30 days after discharge to a hospital within the respective healthcare network. Patients who were coded for any ICD-9/10 admitting diagnosis specifying a pain condition within 30 days of discharge from the index hospital stay were identified. In contrast to principal and secondary diagnoses, the admitting diagnosis usually represents a problem or symptom to describe the main reason for the hospital consultation and is assigned upon arrival prior to the availability of examination and test results (8).

#### Exposures

**Primary.** The primary exposure variable was perioperative abortive migraine treatment. This was defined as a prescription for any medication recommended in the guidelines of the American Headache Society (evidence level A) for acute migraine treatment, which are triptans, ergotamine, analgesics (acetaminophen), and non-steroidal anti-inflammatory drugs (NSAIDs; ibuprofen, diclofenac, aspirin, naproxen) (15). Patients were considered to have received perioperative treatment if the prescription was issued after surgery and within 30 days after discharge from the index hospital stay. For readmitted patients, only prescriptions prior to the readmission day were considered.

**Secondary.** The secondary exposure was preoperatively initiated and perioperatively continued prophylactic migraine treatment. This was defined as a prescription for any medication recommended in the guidelines of the American Headache Society (evidence level A and B) for prophylactic migraine treatment, which are beta-blockers (metoprolol, propranolol, timolol, atenolol, nadolol), antidepressants (amitriptyline, venlafaxine), antiepileptics (divalproex, valproate, topiramate) or onabolulinumtoxin A (16,17). Patients were considered to have received prophylactic treatment if prescriptions were issued within 1 year prior to surgery and in the perioperative period, as described above.

### Statistical analyses

Data management and statistical analyses were conducted utilizing the statistics software STATA version 15 (StataCorp, College Station, TX, USA). If not specified otherwise, continuous, normally distributed variables are expressed as mean (±standard deviation [SD]), continuous, not normally distributed variables as median [interquartile range (IQR)], and categorical variables as frequency counts (percentages). Two-tailed $p$-values $< 0.05$ were considered statistically significant.

#### Primary and secondary analyses

For the primary and secondary analyses, a previously applied multivariable logistic regression model for the same outcome, 30-day pain-related hospital readmission after surgery, was considered (8). To adjust for factors leading to potential confounding of the effects of migraine treatment on pain-related hospital readmission, the following covariates were considered in the model: Sex (dichotomous), age (continuous), body mass index (continuous), ASA physical status ($>3$ versus $\leq 3$, binary) (18), federal insurance coverage (Medicare or Medicaid, yes/no); a patient history of diabetes, substance abuse, chronic obstructive pulmonary disease, affective disorder, anxiety disorder, epilepsy, fibromyalgia, chronic pain, coronary artery disease and stroke (yes/no, respectively); sepsis upon index admission (yes/no), intensive care unit (ICU) stay during index admission (yes/no), adverse discharge disposition (discharge to nursing or other long-term care facility, yes/no), prescription for opioids within 30 days after surgery (yes/no), parameters reflecting surgical complexity such as emergent versus non-emergent surgery (binary), inpatient versus ambulatory surgery (binary), duration of surgery (continuous), work relative value units (continuous) (19), intraoperative hypotensive minutes (mean arterial pressure $< 55$ mmHg, continuous), total intraoperative fluid volume (continuous) (20) and requirement for transfusion of packed red blood cells (yes/no), total intraoperative neuromuscular blocking agent effective dose (continuous) and total intraoperative long-acting morphine equivalent dose (continuous; Supplemental Table 1) (21). The exposure was included as a binary indicator variable differentiating between patients with versus patients without migraine treatment, respectively. Thus, the association between perioperative abortive migraine treatment and 30-day pain-related hospital readmission was assessed as part of the primary analysis. The secondary analysis tested the association between perioperatively continued prophylactic treatment and 30-day pain-related hospital readmission independently of the acute treatment effect. Therefore, perioperative acute migraine treatment was added to the model for the secondary analysis.

#### Exploratory analyses

**Abortive treatment.** In exploratory analyses, the association between the individual migraine drugs that were included in the composite exposure variable of abortive treatment and the outcome pain-related 30-day readmission was tested.

**Opioid treatment.** The effect of perioperative opioid treatment on pain-related hospital readmission after surgery among migraine patients was examined. Perioperative opioid treatment was defined as prescription for any opioid after surgery and within 30 days after discharge from the index hospital stay. If a patient was readmitted, only prescriptions prior to the readmission day were considered. The primary model was applied to test the association between perioperative opioid treatment (exposure) and 30-day pain-related hospital readmission.

**Effect modification.** To assess potential joint effects of abortive and prophylactic treatment, the interaction term "perioperative abortive migraine

treatment*perioperatively continued prophylactic treatment" was tested in the fully adjusted model.

We further considered observed treatment-outcome effects to potentially vary conditional on sex. To test for effect modification by sex, the interaction term "perioperative abortive migraine treatment*sex" was introduced into the primary model.

#### Sensitivity analyses

We performed several sensitivity analyses to evaluate the internal validity of our findings.

Information bias. (i) Outcome misclassification: To account for potential misclassification of the primary admitting diagnosis "pain", the primary analysis was rerun considering 30-day hospital readmission with any primary readmission diagnosis. (ii) Cohort misclassification: In the primary study cohort, migraine patients were identified based on ICD-9/10 diagnosis codes billed at any time prior to surgery. Additionally, we considered triptans and ergotamine to qualify for the identification of migraine patients and redefined our inclusion criteria: Either an ICD-9/10 diagnosis of migraine or a prescription for triptan or ergotamine treatment at any time prior to surgery. The primary analysis was rerun in the redefined study cohort. To account for potential misdiagnosis of migraine as a different headache entity, the primary analysis was rerun in a cohort of patients with a history of any headache diagnosis. To verify whether observed effects were specific to migraine patients, the primary analysis was also rerun in the cohort of patients with a headache diagnosis other than migraine.

Confounding. We performed several additional analyses to address potential residual confounding of the observed treatment-outcome association. Specifically, we addressed the potential bias related to admission status (hospitalized versus ambulatory surgery) and surgical complexity using several analytical strategies: Evaluation of effect measure modification, subgroup analyses, propensity score analyses, and addition of covariates to account for bleeding risk and the surgical trauma intensity (Supplement: sections 3.1–3.4). To evaluate the robustness of our findings towards potential unmeasured confounding, we computed the E-value, a measure introduced by VanderWeele and Ding in 2017 to quantify the minimum magnitude an unmeasured confounder would need to have to fully explain away an observed estimate (22,23). This technique was developed for the risk ratio scale. As our outcome is rare, we considered the estimated odds ratios to closely approximate risk ratios (24).

Further sensitivity analyses including multiple imputations of missing data and model diagnostics are described in the Supplement.

## Results

### Study cohort

A total number of 24,788 adult migraine patients at BIDMC and MGH were reviewed for eligibility. Six patients had an ASA physical status classification of six (brain-death) and 2850 patients had missing data for any covariates of the primary model, and were therefore excluded. There were no missing data for the exposure and outcome variables. The final study cohort included 21,932 patients (Figure 1). In all, 13,027 patients had undergone surgery at BIDMC and 8905 patients at MGH. Overall, 1.4% (n = 302) of patients were readmitted within 30 days after discharge from surgery with an admitting diagnosis specifying pain (Supplemental Table 2). Of all 21,932 patients in the study cohort, 10,921 (49.8%) received perioperative abortive migraine treatment. Table 1 shows the characteristics of the study cohort by treatment status and covariates (Supplemental Table 3 and Supplemental Table 4).

### Primary analysis

In the study cohort, 1.2% (n = 134) of patients with and 1.5% (n = 168) of patients without perioperative abortive treatment were readmitted due to pain within 30 days after discharge (Figure 1). The crude odds ratio (OR) of 30-day pain-related hospital readmission for migraine patients with compared to those without a prescription for perioperative abortive migraine treatment was 0.80 (95% confidence interval [CI] 0.64–1.01). In adjusted analysis, patients with a prescription of any perioperative abortive migraine treatment had lower odds of pain-related 30-day hospital readmission (adjusted OR [aOR] 0.63 [95% CI 0.49–0.81]) (Table 2; Supplemental Table 5).

### Secondary analysis

Of the total number of 21,932 patients in the study cohort, 3678 (16.8%) patients received continued prophylactic migraine treatment. In all, 1.7% (n = 62) of patients with and 1.3% (n = 240) of patients without prophylactic treatment were readmitted due to pain. The crude odds ratio of 30-day pain-related hospital readmission for migraine patients with compared to those without perioperatively continued prophylactic migraine treatment was 1.29 (95% CI 0.97–1.71). In adjusted analysis, there was no significant association between perioperatively continued prophylactic

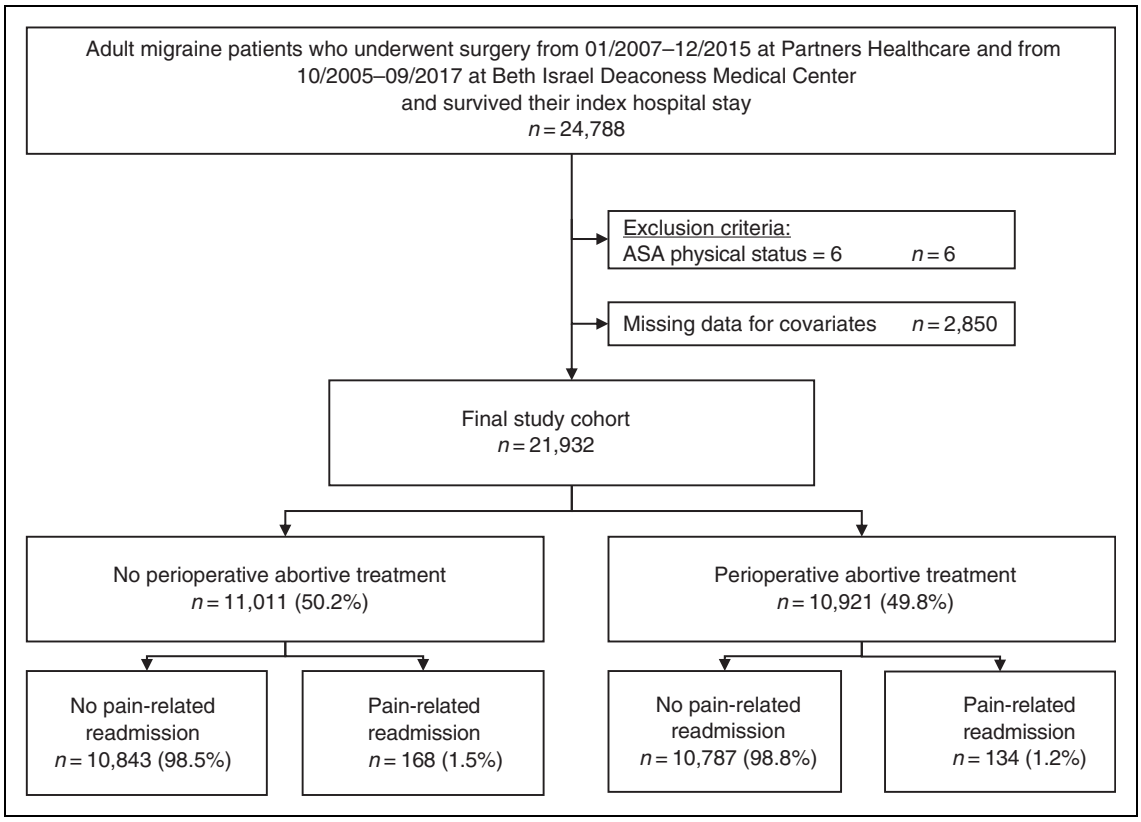


**Figure 1.** Study flow.

migraine treatment and pain-related 30-day readmission independently of the acute treatment effect (aOR 0.97 [95% CI 0.72–1.32]) (Table 2).

## *Exploratory analysis*

*Abortive treatment.* Abortive migraine treatment was defined as a composite of migraine-specific substances (triptans, ergotamine) and analgesics/NSAIDs (acetaminophen, aspirin, naproxen, diclofenac, ibuprofen) as recommended by current guidelines. Of the 21,932 migraine patients, 1810 (8.3%) received perioperative triptan or ergotamine treatment. 0.5% (n = 9) of patients with and 1.5% (n = 293) of patients without perioperative triptan or ergotamine treatment were readmitted for any pain within 30 days of discharge from surgery. The crude odds ratio of 30-day pain-related hospital readmission for patients with compared to those without a perioperative prescription for triptans or ergotamine was 0.34 (95% CI 0.17–0.66). Also in adjusted analysis, perioperative triptan or ergotamine treatment showed a significant protective effect on pain-related 30-day readmission (aOR 0.33 [95% CI 0.17–0.64]) (Table 2). Analgesics/NSAIDs were prescribed to 10,269 (46.8%) of patients. In all, 1.2% (n = 127) of patients with and 1.5% (n = 175) of patients without a perioperative prescription for analgesics/NSAIDs were readmitted for any pain within 30 days of discharge from surgery. The crude odds ratio of 30-day pain-related hospital readmission for patients with compared to those without a perioperative prescription for analgesics/NSAIDs was 0.82 (95% CI 0.65–1.03). In adjusted analysis, a perioperative analgesic/NSAID prescription showed a significant inverse effect on pain-related 30-day readmission (aOR 0.65 [95% CI 0.51–0.84]) (Table 2).

*Opioid treatment.* In our study cohort, 19,035 (86.8%) patients received perioperative opioid treatment. In all, 1.4% (n = 268) of patients with and 1.2% (n = 34) of patients without opioid treatment were readmitted due to pain. Perioperative opioid treatment showed no significant effect on pain-related 30-day readmission both in crude (OR 1.20 [95% CI 0.84–1.72] and adjusted analysis (aOR 0.97 [95% CI 0.67–1.40]) (Table 2).

**Table 1.** Patient baseline characteristics.

| | No perioperative abortive treatment prescription n = 11,011 | Perioperative abortive treatment prescription n = 10,921 |
|---|---|---|
| Demographics | | |
| Age, years | 50.80 ± 14.23 | 49.78 ± 14.13 |
| BMI, kg/m$^2$ | 28.91 ± 7.39 | 29.21 ± 7.78 |
| Sex, female | 8898 (80.8%) | 9137 (83.7%) |
| ASA[a] physical status | 2.00 (2.00, 3.00) | 2.00 (2.00, 3.00) |
| Federal insurance[b] | 3456 (31.4%) | 3573 (32.7%) |
| Index hospital stay | | |
| Inpatient surgery | 4149 (37.7%) | 8024 (73.5%) |
| Emergency surgery | 599 (3.0%) | 50 (2.8%) |
| Adverse discharge[c] | 396 (3.6%) | 616 (5.6%) |
| ICU[d] stay during index admission | 393 (3.6%) | 785 (7.2%) |
| Opioids within 30 days after surgery | 6638 (60.3%) | 8780 (80.4%) |
| Intraoperative factors | | |
| Hypotensive minutes[e] | 0.00 (0.00, 2.00) | 0.00 (0.00, 2.00) |
| Work relative value units[f] | 8.54 (5.45, 15.27) | 15.00 (8.48, 21.79) |
| Duration of surgery, min | 93.00 (56.00, 149.00) | 142.00 (91.00, 219.00) |
| Fluids[h], ml | 1750.00 (1000.00, 2500.00) | 1750.00 (1000.00, 2800.00) |
| NDNMBAs ED[g] | 0.00 (0.00, 2.12) | 2.07 (0.00, 3.40) |
| Packed red blood cells | 154 (1.4%) | 239 (2.2%) |
| Opioids[i] | 31.80 (12.50, 62.50) | 58.50 (31.80, 86.30) |
| Comorbidities (within 1 year prior to surgery) | | |
| Diabetes mellitus | 1751 (15.9%) | 1487 (13.6%) |
| Ischemic stroke | 177 (1.6%) | 334 (3.1%) |
| Coronary artery disease | 1019 (9.3%) | 950 (8.7%) |
| Congestive heart failure | 548 (5.0%) | 544 (5.0%) |
| COPD | 600 (5.4%) | 718 (6.6%) |
| Hypertension | 4544 (41.3%) | 4517 (41.4%) |
| Substance abuse | 1108 (10.1%) | 1477 (13.5%) |
| Sepsis at admission | 15 (0.1%) | 61 (0.6%) |
| Chronic pain | 695 (6.3%) | 866 (7.9%) |
| Anxiety disorder | 1950 (17.7%) | 2667 (24.4%) |
| Affective disorder | 1311 (11.9%) | 1522 (13.9%) |
| Fibromyalgia | 819 (7.4%) | 1074 (9.8%) |
| Epilepsy | 553 (5.0%) | 560 (5.1%) |

Note: Values are provided as frequency (prevalence in %) or mean ± standard deviation or median (interquartile range, values separated by comma).
[a]American Society of Anesthesiologists.
[b]Medicare or Medicaid insurance coverage.
[c]Discharge to nursing facility, long term care or swing bed (skilled nursing facility bed provided by small hospitals).
[d]Intensive Care Unit.
[e]Below mean arterial blood pressure of 55mmHg.
[f]Measure of surgical complexity based on surgical CPT (Current Procedural Terminology) codes.
[g]Multiples of the 95% effective dose equivalent of intraoperatively administered neuromuscular blocking agents.
[h]Crystalloids (0.9% normal saline, lactated ringer's) and colloids (hextend, albumin) in crystalloid-to-colloid ratio 1.5:1.
[i]Morphine oral equivalent dose of long-acting opioids (meperidine, morphine, methadone, hydromorphone).

*Effect modification.* There was no indication for joint effects between perioperative abortive and perioperatively continued prophylactic migraine treatment. In the fully adjusted model, the interaction term between acute and prophylactic treatment was not significant ($p$ for interaction = 0.990). Of note, the primary effect of perioperative acute migraine treatment on 30-day pain-related readmission remained robust (aOR 0.63 [95% CI 0.48–0.84]) in the fully adjusted model complemented by the prophylactic treatment variable and the interaction term between acute and prophylactic treatment.

The effects of perioperative acute migraine treatment on the risk of 30-day pain-related hospital readmission did not vary conditional on sex. The interaction term between perioperative acute treatment and sex was not significant when added to the primary model ($p$ for interaction = 0.474).

**Table 2.** Cumulative incidence, crude and adjusted odds ratios for primary, secondary and exploratory analyses.

| | 30-day readmission for pain; n (%) | Crude odds ratio (95% CI) | Adjusted odds ratio (95% CI) |
|---|---|---|---|
| Primary analysis[a] | | | |
| No perioperative abortive migraine treatment, n = 11,011 (50.2%) | 168 (1.5%) | Reference | Reference |
| Perioperative abortive migraine treatment, n = 10,921 (49.8%) | 134 (1.2%) | 0.80 (0.64–1.01) | 0.63 (0.49–0.81) |
| Secondary analysis[b] | | | |
| No perioperatively continued prophylactic migraine treatment, n = 18,254 (83.2%) | 240 (1.3%) | Reference | Reference |
| Perioperatively continued prophylactic migraine treatment, n = 3678 (16.8%) | 62 (1.7%) | 1.29 (0.97–1.71) | 0.97 (0.72–1.32) |
| Exploratory analyses[a] | | | |
| No perioperative triptan or ergotamine treatment, n = 20,122 (91.7%) | 293 (1.5%) | Reference | Reference |
| Perioperative triptan or ergotamine treatment, n = 1810 (8.3%) | 9 (0.5%) | 0.34 (0.17–0.66) | 0.33 (0.17–0.64) |
| No perioperative analgesics/NSAIDs, n = 11,663 (53.2%) | 175 (1.5%) | Reference | Reference |
| Perioperative analgesics/NSAIDs, n = 10,269 (46.8%) | 127 (1.2%) | 0.82 (0.65–1.03) | 0.65 (0.51–0.84) |
| No perioperative opioid treatment, n = 2897 (13.2%) | 34 (1.2%) | Reference | Reference |
| Perioperative opioid treatment, n = 19,035 (86.8%) | 268 (1.4%) | 1.2 (0.84–1.72) | 0.97 (0.67–1.4) |

[a]Multivariable regression model (last column) includes covariates: Sex, age (continuous), body mass index (continuous), ASA physical status (>3 versus ≤3), federal insurance coverage (Medicare or Medicaid, yes/no); a patient history of diabetes, substance abuse, chronic obstructive pulmonary disease, affective disorder, anxiety disorder, epilepsy, fibromyalgia, chronic pain, coronary artery disease and stroke; sepsis upon index admission, intensive care unit (ICU) stay during index admission, adverse discharge disposition (discharge to nursing or other long-term care facility), prescription for opioids within 30 days after surgery, parameters reflecting surgical complexity such as emergent versus non-emergent surgery, inpatient surgery, duration of surgery (continuous), work relative value units (continuous), intraoperative hypotensive minutes (mean arterial pressure <55 mmHg, continuous), total intraoperative fluid volume (continuous) and requirement for transfusion of packed red blood cells, total intraoperative neuromuscular blocking agent effective dose (continuous) and total intraoperative long-acting morphine equivalent dose (continuous).
[b]Multivariable regression model (last column) includes the same covariates as the primary analysis complemented by perioperative abortive migraine treatment.

## *Sensitivity analysis*

### *Information bias*

Outcome misclassification. In total, 2089 (9.5%) were readmitted to the hospital with any primary readmission diagnosis within 30 days after discharge; 9.8% among patients without and 9.2% among patients with perioperative abortive migraine treatment, respectively. Perioperative abortive treatment was inversely associated with any 30-day readmission (aOR 0.69 [95% CI 0.62–0.76]).

Cohort misclassification. The redefinition of our migraine variable using ICD-9/10 billing codes or triptan or ergotamine treatment increased our study cohort to a total number of 24,949 migraine patients. The results of the primary analysis remained robust in this redefined study cohort (aOR 0.69 [95% CI 0.54–0.88]).

Considering any headache diagnosis, the study cohort measured 62,987 patients. Among any headache patients, perioperative abortive migraine treatment was not significantly associated with 30-day pain-related hospital readmission (aOR 0.87 [95% CI 0.75–1.02]).

Considering only patients with a headache diagnosis other than migraine (n = 41,053), perioperative abortive migraine treatment was not significantly associated with 30-day pain-related hospital readmission (aOR 1.06 [95% CI 0.87–1.28]).

### *Confounding*

Inpatient versus outpatient status. Of the 21,932 migraine patients, 12,173 (55.5%) underwent inpatient procedures. In total, 73.5% of patients with and 37.7% of patients without perioperative abortive treatment underwent inpatient surgery.

We were able to confirm inpatient versus outpatient status to be an important confounding factor of the association between perioperative abortive migraine treatment and post-surgical readmission due to pain. Minimal confounding adjustment only for covariates age (continuous) and inpatient versus outpatient surgery confirmed the findings of our primary analysis (aOR 0.62 [95% CI 0.49–0.79]; $p < 0.001$).

Inpatient versus outpatient status did not modify the association between perioperative abortive treatment and pain-related hospital readmission ($p$ for interaction = 0.958). The primary results remained robust both in the subgroups of migraine patients undergoing inpatient (aOR 0.66 [95% CI 0.49–0.89]) and ambulatory surgery (aOR 0.60 [95% CI 0.36–0.97]). The lack of evidence for effect modification by admission status confirms the reporting of a single summary estimate for

the migraine treatment-pain readmission association across levels of admission status to be valid.

Our primary findings did not change meaningfully when adding hospital length of stay to the model (aOR 0.63 [95% CI 0.49–0.81]).

Surgical service and bleeding risk. Our primary findings did not change meaningfully when adding variable "surgical service" to the model (aOR 0.65 [95% CI 0.50–0.84]).

The effect of perioperative abortive migraine treatment on risk of readmission for pain was not modified by high versus low surgical bleeding risk status ($p$ for interaction = 0.092) (Supplement: section 3.3) (25).

The results of propensity score analyses are described in the Supplement (section 3.4).

Unmeasured confounding. We observed in our primary analysis an adjusted odds ratio of 0.63 (95% CI 0.49–0.81). Therefore, an unmeasured confounder would have to be associated with both the exposure (perioperative prescription of migraine abortive treatment) and the outcome (postoperative readmission due to pain) with an odds ratio – adjusted for all measured confounders – of 2.55 each to fully explain away our observed estimate (23). An unmeasured confounder with a weaker strength of association could not do so (22). To move the confidence interval such that the observed estimate would no longer be statistically significant, an unmeasured confounder would have to be associated with an adjusted odds ratio of 1.77 with both the exposure and the outcome, respectively (23). Based on these analyses, we believe it is unlikely that the unique effects of pain medication prescription on the readmission risk can be explained by unmeasured confounding.

The results of further sensitivity analyses to better understand the implications and robustness of our findings are described in the Supplement sections 3.5–3.14.

## Discussion

In a large cohort of 21,932 migraine patients undergoing surgery at two of the largest healthcare networks in New England, USA, patients with a prescription for guideline recommended abortive migraine treatment in the perioperative period had lower odds of pain-related hospital readmission. This effect was unique to migraine patients and not reproducible among patients with a headache diagnosis other than migraine. The observed association remained consistent after adjustment for a large number of relevant comorbidities and surgery-related risk factors. Migraine-specific abortive treatment (triptans and ergotamine) prescribed in the perioperative period showed the strongest protective effect on the risk of 30-day readmission due to any pain. Prophylactic migraine treatment showed no effect on pain-related readmission rates after surgery and neither did perioperative opioid treatment.

In this cohort of migraine patients undergoing the wide variety of surgical procedures provided at two large healthcare networks, 30-day readmission rates were as high as 9.5%. Hospital readmissions after surgery are frequent and migraine patients have been shown to be at increased risk (7). Our results suggest that migraine patients may benefit from medications recommended for abortive migraine treatment when undergoing surgery. In our cohort, patients who were treated with triptans, ergotamine, acetaminophen or NSAIDs in the perioperative period tended to have more comorbidities and to undergo more complex procedures. In adjusted analyses, the risk of post-surgical hospital readmission due to pain was decreased by over 35% among migraine patients receiving perioperative abortive migraine treatment, despite group differences in patient demographics, surgical risks and comorbidities. The protective effect was strongest for the migraine-specific substances triptans and ergotamine. We speculate that these results represent adequate treatment for a vulnerable cohort exposed to pain triggers in the perioperative period. The role of triptans beyond the treatment of migraine-specific pain mechanisms is yet to be fully understood (26,27). Potential modulation of nociception from peripheral pathways may play a role in post-surgical pain among migraine patients (26,28,29). Studies have shown that migraine may lead to an alteration of pain processing pathways – the cortical dysexcitability may influence perception of pain (30). For example, general body pain, cutaneous allodynia and abdominal pain are symptoms that have been shown to be associated with migraine attacks (31,32). Our data suggest the perioperative period to be a potentially under-recognized period in which optimized migraine treatment strategies may improve patient well-being, and reduce the economic impact of migraine in the context of hospital readmissions.

Perioperatively continued prophylactic migraine treatment such as beta-blockers, antidepressants, antiepileptics and onabolulinumtoxin A showed no significant effect on postoperative pain-related readmission rates independently of acute migraine treatment. Further, there was no joint effect between acute and prophylactic migraine treatment on the risk of 30-day pain-related readmission after surgery. Migraine patients who receive prophylactic treatment are likely subject to chronic or severe and more disabling migraine. Thus, the prophylactic treatment may not be sufficient to treat the post-discharge pain in these patients. Adherence to prophylactic migraine treatment is low and ranges from 26–29% at 6 months after initiation to 20% after 1 year (33).

Perioperative opioid treatment had no effect on 30-day readmission due to pain. High intraoperative opioid application increases the risk of 30-day hospital readmission (21). Previous population-based studies have found the use of opioids to be common in patients with migraine (34). However, opioid use in migraine is typically discouraged (15). Opioid intake is dose-dependently associated with an increase in migraine attack frequency and headache-related disability (34). Furthermore, opioids lead to increased rates of revisits when chosen as abortive migraine treatment in the emergency department (35). Opioid utilization is associated with an increased risk for medication-overuse headache, which migraine patients are specifically vulnerable to, and risk of transformation of episodic migraine to the chronic form (36,37).

Hospital readmissions account for a financial strain on health care systems due to increased and unexpected hospitalization costs as well as utilization of resources. Due to disability, absenteeism and health care utilization, migraine imposes a substantial cost burden among patients, employers and health care providers in the USA (38). As patients with migraine are at increased risk of hospital readmission, health care costs for this condition may be excessive despite a stable prevalence of migraine and a variety of available treatment options for migraine management (38). It is of importance to investigate readmission reasons in patients with migraine and to develop sufficient treatment strategies that may reduce this risk and save excessive costs. Our study shows that perioperative abortive migraine treatment reduces the risk of hospital readmission after surgery. Physicians need to be aware of migraine being an important, but potentially modifiable factor in the context of hospital readmission risk reduction.

This study has limitations to be considered when interpreting the results. Given the administrative nature of the data, inclusion criteria, exposure and outcome definitions were derived from billing and prescription information susceptible to misclassification. Exposure information obtained from prescription data did not capture any details regarding the indication, dosage and individual adherence. Varying indications and treatment adherence have to be considered, especially with regard to prophylactic treatments (39). Our definition of migraine was based on ICD codes, which are a commonly used classification scheme in epidemiologic research. Bias due to misclassification cannot be ruled out and our cohort of surgical patients with a billing diagnosis of migraine may capture a subgroup of patients with more active and bothersome migraine and aura (7). The pattern of error may be more important than the classification accuracy. However, misclassification of migraine and treatment are likely non-differential by outcome status and our findings were robust when considering alternative criteria for cohort and outcome definition. This is an observational study, which raises the concern of confounding of the observed treatment-outcome association as prognostic factors that are related to the outcome likely influenced the treatment decision. The granularity of our validated data repository allowed us to adjust for a broad spectrum of potentially confounding factors. In sensitivity analyses, our findings were robust when accounting for additional residual confounding, as suggested by the reviewers. The E-value for our primary result suggested that unmeasured confounding of considerable magnitude would be required to explain away our observed estimate (22), which we believe is unlikely to be the case. The study uses data from academic medical centers, which may narrow the transportability of findings to community settings. The study cohort, however, represents a large number of migraine patients undergoing the broad spectrum of different inpatient and outpatient surgical procedures provided at two different institutions.

In summary, perioperative abortive migraine treatment showed protective effects on the risk of pain-related hospital readmission after surgery in a large retrospective cohort of 21,932 migraine patients undergoing surgery at two of the largest healthcare networks in New England, USA.

## Clinical implications

- In a large cohort of over 20,000 migraine patients undergoing the broad spectrum of surgeries provided at two large medical centers in Boston, Massachusetts, patients with a perioperative prescription for guideline-recommended abortive migraine drugs were at decreased risk of pain-related hospital readmission.
- Migraine-specific abortive treatment (triptans and ergotamine) prescribed in the perioperative period showed the strongest protective effect on the risk of 30-day readmission due to any pain.
- Perioperatively continued prophylactic migraine treatment showed no effect on the risk of pain-related readmission after surgery independently of acute treatment.
- Perioperative opioid treatment had no effect on the risk of 30-day hospital readmission due to pain.

## Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SA is a consultant for Allergan, Amgen, Biohaven, Eli Lilly, Novartis, Satsuma, Supernus, Percept, Theranica. TTH reports grants from NINDS (PI), grants from NIGMS, personal fees from *Headache*, personal fees from *Anesthesiology*, personal fees from *Cephalalgia*, outside the submitted work. ME has received investigator-initiated study support from MERCK and is serving on the advisory board for Sugammadex at MERCK.

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