**The Association between General Anesthesia and New Postoperative Uses of Sedative–Hypnotics: A Nationwide Matched Cohort Study**

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**Abstract:** Sedative–hypnotic misuse is associated with psychiatric diseases and overdose deaths. It remains uncertain whether types of anesthesia affect the occurrence of new postoperative uses of sedative–hypnotics (NPUSH). We used reimbursement claims data of Taiwan’s National Health Insurance and conducted propensity score matching to compare the risk of NPUSH between general and neuraxial anesthesia among surgical patients who had no prescription of oral sedative–hypnotics or diagnosis of sleep disorders within the 12 months before surgery. The primary outcome was NPUSH within 180 days after surgery. Multivariable logistic regression models were used to calculate the adjusted odds ratio (aOR) and 95% confidence interval (CI). A total of 92,222 patients were evaluated after matching. Among them, 15,016 (16.3%) had NPUSH, and 2183 (4.7%) were made a concomitant diagnosis of sleep disorders. General anesthesia was significantly associated both with NPUSH (aOR: 1.17, 95% CI: 1.13–1.22, p < 0.0001) and NPUSH with sleep disorders (aOR: 1.11, 95% CI: 1.02–1.21, p = 0.0212) compared with neuraxial anesthesia. General anesthesia was also linked to NPUSH that occurred 90–180 days after surgery (aOR: 1.12, 95% CI: 1.06–1.19, p = 0.0002). Other risk factors for NPUSH were older age, female, lower insurance premium, orthopedic surgery, specific coexisting diseases (e.g., anxiety disorder), concurrent medications (e.g., systemic steroids), postoperative complications, perioperative blood transfusions, and admission to an intensive care unit. Patients undergoing general anesthesia had an increased risk of NPUSH compared with neuraxial anesthesia. This finding may provide an implication in risk stratification and prevention for sedative–hypnotic dependence after surgery.

**Keywords:** anxiolytic; benzodiazepine; risk factor; sleep disorder; sleep disturbance
1. Introduction

Sedative–hypnotic misuse is a growing public health problem, affecting about 2–3% of the adult population worldwide [1,2]. Epidemiological study has shown that benzodiazepines and Z-drugs (i.e., zopiclone and zolpidem) were the third most commonly misused drugs in the United States in 2017 [1,2]. Sedative–hypnotic misuse is associated with psychiatric disorders, impaired quality of life, and overdose deaths [3,4]. However, the initial source of sedative–hypnotics among long-term users remains poorly understood.

Mounting evidence has shown that surgery, general anesthesia, opioids, and pain may contribute to the development of postoperative sleep disturbances by disrupting the sleep/wake cycle and changing sleep architecture [5–13]. Opioids used in general anesthesia can significantly reduce the time percentage of deep sleep and induce or exacerbate both central and obstructive sleep apnea [6–8]. An animal model demonstrated that sevoflurane inhalation induced rapid-eye-movement (REM) sleep deficits, delayed REM sleep recovery, and reduced latency to REM sleep [9]. In contrast, regional anesthesia reduces perioperative opioid consumption and alleviates postoperative pain, which may improve the sleep quality of surgical patients [7,10]. Nevertheless, some studies reported that sleep disturbances occur regardless of reduced opioid consumption and adequate pain relief among patients receiving neuraxial anesthesia [11–13].

Although both general and neuraxial anesthesia potentially relate to postoperative sleep disturbances, no study has compared the rates of postoperative sedative–hypnotic prescriptions between these two anesthetic techniques. Wright et al. recently reported that perioperative uses of benzodiazepines were associated with postoperative persistent uses of benzodiazepines, which may develop into long-term sedative–hypnotic misuse [14]. However, the perioperative influential factors for postoperative sedative–hypnotic uses are largely unknown.

We utilized Taiwan’s National Health Insurance (NHI) research database to conduct a nationwide population-based cohort study. There were two objectives in this study. First, we aimed to compare the risk of new postoperative uses of sedative–hypnotics (NPUSH) between general and neuraxial anesthesia in surgical patients. Second, we sought to evaluate the perioperative risk factors for NPUSH to identify potentially modifiable factors. This may provide important evidence in reducing postoperative sedative–hypnotic uses and preventing long-term misuse and its adverse effects among surgical patients. Based on the current evidence [5–10], we hypothesized that general anesthesia was associated with higher risks of NPUSH and new-onset sleep disorders compared with neuraxial anesthesia.

2. Material and Methods

2.1. Source of Data

This study obtained the approval from the Institutional Review Board of Taipei Medical University in Taiwan (TMU-JIRB-N202101005; data of approval on 7 January 2021). Written informed consent was waived by the Institutional Review Board. All methods of this study were performed in accordance with relevant guidelines and regulations [15]. Taiwan’s National Health Insurance program was launched in March 1995 and offered insurance to more than 99% of 23.5 million Taiwanese residents. The NHI research database contains comprehensive data of the insured beneficiaries, including demographic characteristics (e.g., date of birth and sex) and claims data (e.g., medical diagnoses, prescription drugs, interventional or diagnostic procedures, and medical expenditures). The NHI research data have been broadly used in epidemiological studies [16–18]. This study used three Longitudinal Health Insurance Databases (LHID2000, LHID2005, and LHID2010), which randomly sampled 1 million people from the original NHI research database in the years 2000, 2005, and 2010, respectively. The representativeness of LHIDs has been validated by Taiwan’s National Health Research Institutes [19].
2.2. **Patient Selection**

We used the medical claims of 3 million insured individuals to select patients who were aged \( \geq 20 \) years and underwent their first surgery requiring general or neuraxial anesthesia from 1 January 2002 to 30 June 2013. We excluded surgeries that could only be performed with general anesthesia, surgeries with a length of hospital stay < 2 days, patients who were prescribed any oral sedative–hypnotics or had any diagnoses of sleep disorders within 12 months before the index surgery, and patients who died within 180 days after the index surgery. Oral sedative–hypnotics included benzodiazepine drugs (diazepam, chlorodiazepoxide, lorazepam, bromazepam, alprazolam, medazepam, oxazepam, fludiazepam, oxazolam, nitrazepam, flunitrazepam, lormetazepam, estazolam, triazolam, brotizolam, midazolam, nimetazepam, flurazepam, and clonazepam) and non-benzodiazepine drugs (zopiclone and zolpidem). Each patient with general anesthesia was randomly matched to a patient with neuraxial anesthesia, using a frequency-matched-pair procedure [20].

2.3. **Study Outcome**

The primary outcome was NPUSH within 180 days after surgery. The secondary outcomes were NPUSH with a concomitant diagnosis of sleep disorders within 180 days after surgery, NPUSH which occurred 90–180 days after surgery, and NPUSH within 30, 60, 90, 120, and 150 days after surgery. We identified patients who had a postoperative diagnosis of sleep disorder using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes [21] (Supplementary Table S1).

2.4. **Patient and Clinical Characteristics**

Insurance premium was classified into $0–$500, $501–$800, and > $800 United States dollars per month. Surgeries were classified into orthopedic (lower extremity), genitourinary, anorectal, obstetric (including cesarean section), and hernia repair surgeries. The ICD-9-CM codes of physicians’ diagnoses within 24 months prior to surgery were used to ascertain the following coexisting diseases, chosen based on data availability, physiological plausibility, and the existing literature: hypertension, diabetes mellitus, ischemic heart disease, atherosclerosis, heart failure, cerebrovascular disease, chronic kidney disease, chronic obstruction pulmonary disease, malignancy, anxiety disorder, depressive disorder, schizophrenia, and bipolar disorder [22] (Supplementary Table S1). Lifestyle factors included obesity, smoking disorder, alcohol-use disorder, other substance-use disorder, and malnutrition [22]. The numbers of hospitalizations and emergency visits within 24 months before the index surgery were examined to reflect patients’ overall health and to avoid ascertainment bias. We also evaluated the requirements for blood transfusion (red blood cells, fresh frozen plasma, or platelets) [23,24] and intensive care during the index surgical admission. Major complications that occurred within 30 days after the index surgery were analyzed, including pneumonia, septicemia, acute renal failure, pulmonary embolism, deep vein thrombosis, stroke, urinary tract infection, surgical site infection, acute myocardial infarction, cardiac dysrhythmias, and postoperative bleeding. The analyses also adjusted for the concurrent medications prescribed within 180 days after the surgery which might cause sleep disorders, including systemic steroids, ephedrine, theophylline, diuretics, and anti-depressants [25]. Diuretics included furosemide, bumetanide, torsemide, spironolactone, and chlorothiazide. Anti-depressants were comprised of selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline, fluvoxamine, and escitalopram) and serotonin norepinephrine reuptake inhibitors (venlafaxine and duloxetine).

2.5. **Statistical Analysis**

Continuous variables were summarized using mean ± standard deviation. Categorical variables were expressed as frequency and percentage. A non-parsimonious multivariable logistic regression model was used to estimate a propensity score for subjects undergoing general or neuraxial anesthesia. We matched each patient with general anesthesia to a patient with neuraxial anesthesia using a greedy matching algorithm within a tolerance
limit of 0.05 and without replacement to balance the distributions of age, sex, insurance premium, types of surgery, coexisting diseases, lifestyle factors, concurrent medications, numbers of hospitalizations and emergency visits before surgery, postoperative complications, perioperative blood transfusions, and admission to intensive care units (ICU) between the two groups [20]. The distributions of baseline patient characteristics were compared between matched pairs by using the standardized difference [26]. Multivariable logistic regression analyses were used to adjust for all included variables and to calculate the adjusted odds ratio (aOR) and 95% confidence interval (CI) for the outcome of interest. Kaplan–Meier curves and log-rank tests were used to compare the cumulative incidence of NPUSH within 180 days after surgery between the groups. Subgroup analyses were also conducted by age, sex, coexisting diseases, concurrent medications, postoperative complications, blood transfusions, and admission to the ICU. Sensitivity analyses were conducted by excluding patients who had a history of anxiety disorder, depressive disorder, schizophrenia, bipolar disorder, alcohol-use disorder, other substance-use disorder, or uses of anti-depressants (Analysis I), excluding patients with a history of malignancy (Analysis II), and excluding patients with perioperative uses of blood transfusion, postoperative complications, or ICU admission (Analysis III). We considered a two-sided level of 0.05 statistically significant. All the statistical analyses were conducted using Statistics Analysis System (SAS), Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline Patient Characteristics

The patient selection and matching process generated 46,111 matched pairs for analysis. (Figure 1) Table 1 shows the baseline patient characteristics. Notably, the distributions of demographics, types of surgery, coexisting diseases, lifestyle factors, concurrent medications, number of hospitalizations, number of emergency room visits, postoperative complications, perioperative blood transfusions, and admissions to ICUs were well balanced after matching.

3.2. New Postoperative Uses of Sedative–Hypnotics

In the postoperative 180-day period, 15,016 patients (16.3%) had NPUSH and 2183 (4.7%) had a concomitant diagnosis of sleep disorders. Table 2 shows the results of univariate and multivariable logistic regression analyses for NPUSH. General anesthesia was significantly associated with a higher risk of NPUSH compared with neuraxial anesthesia (aOR: 1.17, 95% CI: 1.13–1.22, \( p < 0.0001 \); absolute risk difference: 0.024, 95% CI: 0.017–0.030; Figure 2). The time to NPUSH was median 47 days (interquartile range: 19–100) for patients with general anesthesia and 44 (16–103) for those with neuraxial anesthesia. Sensitivity analyses showed similar results: Analysis I (aOR: 1.18, 95% CI: 1.14–1.23, \( p < 0.0001 \)), Analysis II (aOR: 1.17, 95% CI: 1.12–1.21, \( p < 0.0001 \)), and Analysis III (aOR: 1.18, 95% CI: 1.13–1.22, \( p < 0.0001 \)). In addition, general anesthesia was associated with increased NPUSH with sleep disorders (aOR: 1.11, 95% CI: 1.02–1.21, \( p = 0.0212 \)). General anesthesia was also linked to NPUSH which occurred 90–180 days after surgery (aOR: 1.12, 95% CI: 1.06–1.19, \( p = 0.0002 \)) (Table 3).
|                                      | GA  | NA  | SDD |
|--------------------------------------|-----|-----|-----|
| Age (years), mean (SD)               | 50.0| 50.0| <0.0001 |
| Sex, male, n (%)                     | 25,607| 25,544| 0.0030 |
| Insurance premium (USD/month), n (%) | 18,408| 18,477| -0.0004 |
| 0–500                                | 39.9| 40.1| |
| 501–800                              | 33.6| 33.2| |
| >801                                 | 26.5| 26.7| |
| Type of surgery, n (%)               | 18,915| 18,957| -0.0021 |
| Orthopedic, lower extremity          | 41.0| 41.1| |
| Genitourinary                        | 25.8| 25.6| 0.0053 |
| Anorectal                            | 12.0| 11.8| 0.0127 |
| Obstetric                            | 12.9| 12.9| 0.0012 |
| Hernia repair                        | 8.5| 8.9| -0.0277 |
| Coexisting diseases, n (%)           | 11,001| 11,013| -0.0008 |
| Hypertension                         | 23.9| 23.9| |
| Diabetes mellitus                    | 11.5| 11.6| -0.0043 |
| Ischemic heart disease               | 7.0| 7.1| -0.0058 |
| Atherosclerosis                      | 0.6| 0.6| 0.0229 |
| Heart failure                        | 2.1| 2.1| 0.0030 |
| Cerebrovascular disease              | 5.4| 5.3| 0.0052 |
| Chronic kidney disease               | 3.5| 3.4| 0.0149 |
| COPD                                 | 6.1| 6.3| -0.0123 |
| Malignancy                           | 5.1| 5.3| -0.0211 |
| Anxiety disorder                     | 3.7| 3.7| 0.0030 |
| Depressive disorder                  | 0.2| 0.2| -0.0401 |
| Schizophrenia                        | 0.2| 0.2| 0.0211 |
| Bipolar disorder                     | 0.1| 0.1| -0.0526 |
| Obesity                              | 0.5| 0.5| 0.0048 |
| Smoking disorder                     | 0.6| 0.6| -0.0020 |
| Alcohol-use disorder                 | 0.9| 0.9| 0.0068 |
| Other substance-use disorder         | 0.02| 0.02| 0 |
| Malnutrition                         | 0.5| 0.5| 0.0259 |
| Concurrent medications, n (%)        | 6725| 6703| 0.0021 |
| Systemic steroids                    | 14.6| 14.5| |
| Ephedrine                            | 7302| 7444| -0.0126 |
| Theophylline                          | 15.8| 16.1| |
| Diuretics                            | 81| 83| -0.0117 |
| Anti-depressants                      | 8.4| 8.4| -0.0025 |
| Number of hospitalizations, n (%)     | 3867| 3883| |
| 0                                   | 860| 860| 0.0062 |
| 1                                   | 132| 132| |
| ≥3                                  | 312| 312| |
| Number of ER visits, n (%)           | 793| 802| 0.0090 |
| 0                                   | 37,741| 37,926| 82.3|
| 1                                   | 6085| 5971| 13.0|
| ≥3                                  | 2834| 2950| 6.4|
| Blood transfusion, n (%)             | 1797| 1796| 23.4|
| Postoperative complications, n (%)   | 560| 487| 1.1|
| ICU admission, n (%)                 | 526| 5422| 11.8|

Abbreviation: COPD = chronic obstruction pulmonary disease; ER = emergency room; GA = general anesthesia; ICU = intensive care unit; NA = neuraxial anesthesia; SD = standard deviation; SDD = standardized difference; USD = United States dollar.
3.2. New Postoperative Uses of Sedative–Hypnotics

In the postoperative 180-day period, 15,016 patients (16.3%) had NPUSH and 2183 (4.7%) had a concomitant diagnosis of sleep disorders. Table 2 shows the results of uni-/multivariable logistic regression analyses for NPUSH. General anesthesia was significantly associated with a higher risk of NPUSH compared with neuraxial anesthesia (aOR: 1.17, 95% CI: 1.13–1.22, \( p < 0.0001 \); absolute risk difference: 0.024, 95% CI: 0.017–0.030; Figure 2). The time to NPUSH was median 47 days (interquartile range: 19–100) for patients with general anesthesia and 44 (16–103) for those with neuraxial anesthesia. Sensitivity analyses showed similar results: Analysis I (aOR: 1.18, 95% CI: 1.14–1.23, \( p < 0.0001 \)), Analysis II (aOR: 1.17, 95% CI: 1.12–1.21, \( p < 0.0001 \)), and Analysis III (aOR: 1.18, 95% CI: 1.13–1.22, \( p < 0.0001 \)). In addition, general anesthesia was associated with increased NPUSH with sleep disorders (aOR: 1.11, 95% CI: 1.02–1.21, \( p = 0.0212 \)). General anesthesia was also linked to NPUSH which occurred 90–180 days after surgery (aOR: 1.12, 95% CI: 1.06–1.19, \( p = 0.0002 \)) (Table 3).

Figure 1. Flow diagram for patient selection.
Figure 2. Cumulative incidence of new postoperative uses of sedative–hypnotics (NPUSH) between patients undergoing general and neuraxial anesthesia with number of subjects at risk.

Table 2. Univariate and multivariable analyses for new postoperative uses of sedative–hypnotics.

|                          | Univariate | Multivariable |
|--------------------------|------------|---------------|
|                          | OR         | 95% CI        | p      | OR         | 95% CI        | p      |
| GA vs. NA                | 1.15       | 1.11–1.19     | <0.0001 | 1.17       | 1.13–1.22     | <0.0001 |
| Age (years)              | 1.03       | 1.02–1.03     | <0.0001 | 1.01       | 1.01–1.01     | <0.0001 |
| Sex, male vs. female     | 0.85       | 0.83–0.89     | <0.0001 | 0.80       | 0.76–0.83     | <0.0001 |
| Insurance premium (USD/month) | <0.0001 | <0.0001 | <0.0001 | 0.81       | 0.78–0.84     | <0.0001 |
| 501–800 vs. 0–500        | ≥801 vs. 0–500 | <0.0001 | <0.0001 | 0.50       | 0.47–0.52     | <0.0001 |
| Type of surgery          |            |               |        |            |               |        |
| Orthopedic, lower extremity | 1.79      | 1.73–1.85     | <0.0001 | 1.44       | 1.04–2.01     | 0.0303 |
| Genitourinary            | 1.04       | 1.00–1.08     | 0.0823  | 1.04       | 0.75–1.45     | 0.7960 |
| Anorectal                | 0.75       | 0.70–0.79     | <0.0001 | 1.08       | 0.78–1.51     | 0.6460 |
| Obstetric                | 0.34       | 0.31–0.36     | <0.0001 | 0.50       | 0.36–0.71     | <0.0001 |
| Hernia repair            | 0.64       | 0.59–0.69     | <0.0001 | 0.79       | 0.57–1.10     | 0.1610 |
| Coexisting diseases      |            |               |        |            |               |        |
| Hypertension             | 1.81       | 1.74–1.88     | <0.0001 | 0.96       | 0.92–1.01     | 0.1280 |
| Diabetes mellitus        | 1.67       | 1.59–1.75     | <0.0001 | 1.06       | 1.00–1.12     | 0.0555 |
| Ischemic heart disease   | 1.91       | 1.80–2.02     | <0.0001 | 1.15       | 1.07–1.23     | <0.0001 |
| Atherosclerosis          | 2.16       | 1.79–2.60     | <0.0001 | 1.18       | 0.96–1.44     | 0.1142 |
| Heart failure            | 2.02       | 1.82–2.23     | <0.0001 | 0.86       | 0.77–0.97     | 0.0122 |
| Cerebrovascular disease  | 1.77       | 1.66–1.90     | <0.0001 | 0.93       | 0.86–1.00     | 0.0608 |
| Chronic kidney disease   | 1.64       | 1.51–1.79     | <0.0001 | 0.95       | 0.86–1.04     | 0.2863 |
| COPD                     | 1.82       | 1.71–1.93     | <0.0001 | 1.10       | 1.02–1.18     | 0.0106 |
| Malignancy               | 1.62       | 1.51–1.74     | <0.0001 | 1.22       | 1.13–1.31     | <0.0001 |
| Anxiety disorder         | 1.82       | 1.68–1.97     | <0.0001 | 1.46       | 1.34–1.59     | <0.0001 |
| Depressive disorder      | 1.85       | 1.34–2.55     | 0.0002  | 1.02       | 0.70–1.47     | 0.9374 |
| Schizophrenia            | 2.41       | 1.72–3.37     | <0.0001 | 1.85       | 1.28–2.67     | 0.0010 |
| Bipolar disorder         | 3.17       | 1.90–5.27     | <0.0001 | 1.76       | 0.98–3.17     | 0.0586 |
Table 2. Cont.

| Lifestyle factors | Univariate | Multivariable |
|-------------------|------------|--------------|
| Obesity           | cOR 1.29   | aOR 1.16     |
|                   | 95% CI 1.03–1.63 | 95% CI 0.91–1.48 |
| Smoking disorder  | 1.00       | 1.12         |
|                   | 95% CI 0.80–1.26 | 95% CI 0.89–1.41 |
| Alcohol-use disorder | 1.82     | 1.75         |
|                   | 95% CI 1.56–2.13 | 95% CI 1.48–2.06 |
| Other substance-use disorder | 5.15     | 4.95         |
|                   | 95% CI 1.93–13.71 | 95% CI 1.78–13.72 |
| Malnutrition      | 1.44       | 0.93         |
|                   | 95% CI 1.16–1.80 | 95% CI 0.73–1.18 |

Table 3. New postoperative uses of sedative–hypnotics for patients undergoing general or neuraxial anesthesia.

| GA | NA | NPUSH risk |
|----|----|------------|
| Event | Rate (%) | Event | Rate (%) | aOR (95% CI) † | p |
| All NPUSH | 7938 | 17.2 | 7078 | 15.4 | 1.17 (1.13–1.22) | <0.0001 |
| NPUSH with sleep disorder | 1135 | 2.5 | 1048 | 2.3 | 1.11 (1.02–1.21) | 0.0212 |
| 30-day NPUSH | 3011 | 6.5 | 2943 | 6.4 | 1.03 (0.98–1.09) | 0.2527 |
| 60-day NPUSH | 4587 | 10.0 | 4107 | 8.9 | 1.15 (1.10–1.20) | <0.0001 |
| 90-day NPUSH | 5640 | 12.2 | 4994 | 10.8 | 1.17 (1.12–1.22) | <0.0001 |
| 120-day NPUSH | 6539 | 14.2 | 5760 | 12.5 | 1.18 (1.14–1.23) | <0.0001 |
| 150-day NPUSH | 7279 | 15.8 | 6436 | 14.0 | 1.18 (1.14–1.23) | <0.0001 |
| 90–180-day NPUSH | 2338 | 5.1 | 2111 | 4.6 | 1.12 (1.06–1.19) | 0.0002 |

Abbreviation: aOR = adjusted odds ratio; COPD = chronic obstructive pulmonary disease; cOR = crude odds ratio; ER = emergency room; GA = general anesthesia; ICU = intensive care unit; NA = neuraxial anesthesia; USD = United States dollar.

Other independent factors for NPUSH were age (aOR: 1.01), sex (male vs. female, aOR: 0.80), insurance premium ($501–800 USD/month vs. 0–500: aOR: 0.95; ≥ 801 vs. 0–500, aOR: 0.79), orthopedic surgery (aOR: 1.44), and obstetric surgery (aOR: 0.50). Coexisting diseases related to NPUSH were ischemic heart disease (aOR: 1.15), heart failure (aOR: 0.86), chronic obstructive pulmonary disease (aOR: 1.10), malignancy (aOR: 1.22), anxiety disorder (aOR: 1.46), schizophrenia (aOR: 1.85), alcohol-use disorder (aOR: 1.75), and other substance-use disorder (aOR: 4.95). Patients using the following medications had a higher risk of NPUSH: systemic steroids (aOR: 1.81), ephedrine (aOR: 1.31), theophylline (aOR: 1.27), diuretics (aOR: 1.88), and anti-depressants (aOR: 16.09). In addition, perioperative complications increased the risk of NPUSH. The patients undergoing general anesthesia were more at risk of NPUSH compared to those undergoing neuraxial anesthesia. The incidence of NPUSH was associated with age, sex, insurance premium, types of surgery, coexisting diseases, lifestyle factors, concurrent medications, number of hospitalizations, number of emergency room visits, perioperative uses of blood transfusion, postoperative complications, and intensive care unit care.
blood transfusion (aOR: 2.06), postoperative complications (aOR: 1.29), and ICU admission (aOR: 1.93) were significantly associated with NPUSH. (Table 2)

3.3. Subgroup Analyses

General anesthesia was associated with NPUSH compared with neuraxial anesthesia in the subgroups of age < 65 years (aOR: 1.25), no malignancy history (aOR: 1.17), no preoperative anxiety disorder (aOR: 1.19), no use of ephedrine (aOR: 1.21), no use of anti-depressants (aOR: 1.17), no perioperative use of blood transfusion (aOR: 1.17), and no admission to an ICU (aOR: 1.18) (Table 4).

Table 4. Subgroup analyses of new postoperative uses of sedative–hypnotics for patients undergoing general or neuraxial anesthesia.

| Subgroup                  | Event Rate (%) | aOR (95% CI)† | p     |
|---------------------------|----------------|---------------|-------|
| Age ≥ 65 years GA         | 2789           | 25.0          | 1.03 (0.97–1.10) | 0.3518 |
| Age ≥ 65 years NA         | 2941           | 24.7          | reference   | <0.0001 |
| Age < 65 years GA         | 5149           | 14.7          | 1.25 (1.20–1.31) | reference |
| Age < 65 years NA         | 4137           | 12.1          | reference   | <0.0001 |
| Male GA                   | 4143           | 16.2          | 1.13 (1.08–1.19) | reference |
| Male NA                   | 3695           | 14.5          | reference   | <0.0001 |
| Female GA                 | 3795           | 18.5          | 1.20 (1.14–1.27) | reference |
| Female NA                 | 3383           | 16.5          | reference   | <0.0001 |
| Malignancy history GA     | 568            | 24.2          | 1.15 (1.00–1.33) | 0.0566 |
| Malignancy history NA     | 554            | 22.7          | reference   | <0.0001 |
| No malignancy history GA  | 7370           | 16.8          | 1.17 (1.12–1.21) | reference |
| No malignancy history NA  | 7327           | 16.8          | reference   | <0.0001 |
| Anxiety disorder GA       | 6524           | 14.9          | reference   | 0.09 (0.77–1.06) |
| Anxiety disorder NA       | 421            | 24.4          | reference   | 0.1962 |
| No anxiety disorder GA    | 7517           | 16.9          | 1.19 (1.14–1.23) | reference |
| No anxiety disorder NA    | 6618           | 14.9          | reference   | <0.0001 |
| Use of systemic steroids GA | 1964       | 29.2          | 1.16 (1.07–1.26) | 0.0003 |
| Use of systemic steroids NA | 1784       | 26.6          | reference   | <0.0001 |
| No use of systemic steroids GA | 5974       | 15.2          | 1.17 (1.12–1.22) | reference |
| No use of systemic steroids NA | 5294       | 13.4          | reference   | <0.0001 |
| Use of ephedrine GA       | 1425           | 19.5          | 1.02 (0.90–1.11) | 0.6935 |
| Use of ephedrine NA       | 1399           | 18.8          | reference   | <0.0001 |
| No use of ephedrine GA    | 6513           | 16.8          | 1.21 (1.16–1.26) | reference |
| No use of ephedrine NA    | 460            | 26.8          | reference   | <0.0001 |
| Use of theophylline GA    | 954            | 25.4          | 1.12 (1.01–1.25) | 0.0387 |
| Use of theophylline NA    | 918            | 24.0          | reference   | <0.0001 |
| No use of theophylline GA | 6984           | 16.5          | 1.18 (1.13–1.22) | <0.0001 |
| No use of theophylline NA | 1640           | 14.6          | reference   | <0.0001 |
| Use of diuretics GA       | 1298           | 33.4          | 1.33 (1.04–1.69) | 0.0116 |
| Use of diuretics NA       | 6538           | 15.5          | reference   | <0.0001 |
| No use of diuretics GA    | 5780           | 13.7          | reference   | <0.0001 |
| No use of diuretics NA    | 283            | 79.5          | 1.18 (0.79–1.75) | 0.4150 |
| Use of anti-depressants GA | 262            | 72.8          | reference   | <0.0001 |
| Use of anti-depressants NA | 262           | 72.8          | reference   | <0.0001 |
| Postoperative complications GA | 1271   | 24.8          | 1.17 (1.07–1.29) | 0.0011 |
| Postoperative complications NA | 1196   | 22.1          | reference   | <0.0001 |
| No postoperative complications GA | 6667  | 16.3          | 1.17 (1.13–1.22) | <0.0001 |
| No postoperative complications NA | 5882  | 14.5          | reference   | <0.0001 |
| Blood transfusion GA      | 272            | 48.6          | 1.09 (0.84–1.43) | 0.5240 |
| Blood transfusion NA      | 226            | 46.4          | reference   | <0.0001 |
| No blood transfusion GA   | 7666           | 16.8          | 1.17 (1.13–1.22) | <0.0001 |
| No blood transfusion NA   | 6852           | 15.0          | reference   | <0.0001 |
| ICU admission GA          | 124            | 44.9          | 0.77 (0.50–1.20) | 0.2494 |
| ICU admission NA          | 117            | 46.6          | reference   | <0.0001 |
| No ICU admission GA       | 7814           | 17.1          | 1.18 (1.13–1.22) | <0.0001 |
| No ICU admission NA       | 6961           | 15.2          | reference   | <0.0001 |

Abbreviation: aOR = adjusted odds ratio; CI = confidence interval; GA = general anesthesia; ICU = intensive care unit; NA = neuraxial anesthesia. † Adjusted for age (continuous), sex, insurance premium (categorical), types of surgery, coexisting diseases, lifestyle factors, concurrent medications, number of hospitalizations, number of emergency room visits, perioperative uses of blood transfusion, postoperative complications, and intensive care unit care.
4. Discussion

The present study demonstrated that general anesthesia was associated with greater NPUSH compared with neuraxial anesthesia. The NPUSH risk associated with general anesthesia persisted 90 to 180 days after surgery. Our analyses identified some potentially modifiable factors for NPUSH, which may contribute to risk stratification and prevention before surgery. This study has several strengths to evaluate the putative effect of general anesthesia on NPUSH. First, we used a nationwide dataset to increase the patient sample and to cover the medical institutions of different levels, which increases the generalizability of the study results. Second, we used a propensity-score-matching analysis to balance the distributions of various patient and clinical factors and to minimize potential confounding effects. Our results suggest that types of anesthesia may impact the risk of new prescriptions of sedative–hypnotics among surgical patients, providing an implication in preventing the long-term misuse of these drugs.

This study is the first to compare the risk of NPUSH between general and neuraxial anesthesia among surgical patients. Most of the previous studies focused on polysomnography parameters instead of pragmatic outcomes (e.g., sedative–hypnotic prescriptions) [6–9,11–13]. In addition, prior studies did not evaluate the potential impact of different anesthesia techniques on sleep disturbances and sedative–hypnotic uses [6,8–13]. Our results suggested that patients receiving neuraxial anesthesia did have NPUSH and sleep disorders, but the risk was significantly lower than that of general anesthesia. Previous studies reported several risk factors for postoperative sleep disorders, including older age [8,27], more extensive surgical trauma [28], and longer length of hospital stay [10]. A recent study showed that perioperative benzodiazepine use was associated with postoperative persistent benzodiazepine use [14]. Our study added important evidence to the current literature by identifying more risk factors for NPUSH, including orthopedic surgery, preexisting malignancy and anxiety disorder, concurrent uses of systemic steroids, ephedrine, theophylline, diuretics, and anti-depressants, perioperative blood transfusion, postoperative complications, and admission to ICUs.

We proposed the following possible explanations for our findings. First, opioids and volatile anesthetics used in general anesthesia may disrupt the sleep/wake cycle and other circadian rhythms (e.g., melatonin secretion and body temperature) [5–9], although it remains controversial whether neuraxial anesthesia effectively reduces the postoperative uses of opioids [29]. Song and colleagues recently showed that subarachnoid anesthesia was related to less impairment of melatonin circadian rhythms and sleep patterns among elderly patients undergoing hip-fracture surgery [30]. Second, pain intensity is an established determinant for postoperative sleep quality, and vice versa [31,32]. Regional anesthesia has proven effective in reducing postoperative acute and chronic pain [33,34]. Third, surgery requiring general anesthesia might reflect the longer operative duration and more extensive surgical injury, which were potentially related to the complicated postoperative course and sleep deprivation. Noticeably, our results have been controlled for postoperative complications and the need for intensive care in the analytical model.

A database study showed that 15.2% and 4.9% of patients with new benzodiazepine prescriptions continued to use benzodiazepines for 1 year and 8 years, respectively [35]. Additionally, postoperative sleep deprivation is associated with delirium, higher sensitivity to pain, and longer length of hospital stay [10,31,36]. However, there are still few prophylactic and therapeutic measures to reduce postoperative sedative–hypnotic uses and to improve postoperative sleep quality. Avoiding perioperative benzodiazepine use may prevent persistent benzodiazepine use after surgery [14]. Furthermore, some clinical strategies have been developed to improve postoperative sleep, including laparoscopic techniques [37], melatonin supplementation [38], and dexmedetomidine infusion [39]. A clinical trial recently reported that propofol-based general anesthesia might promote postoperative sleep quality compared with volatile general anesthesia [40]. Our results indicated that regional anesthesia might protect surgical patients against postoperative
sedative–hypnotic uses and sleep disorders, although the effect size appeared modest after adjustment for covariates.

The present study identified several modifiable risk factors for NPUSH. First, systemic corticosteroids, ephedrine, and diuretics are commonly used in the perioperative period. More studies are needed to evaluate their potential impact and threshold dose for postoperative sleep disturbances and NPUSH. Second, perioperative allogeneic blood transfusion has been found to trigger systemic inflammation and potentially exert a detrimental effect on postoperative outcome [41]. In addition, the need for blood transfusion might reflect the longer duration of surgery and greater extent of surgical trauma. It is important to take the risks of NPUSH and sleep disorders into account when blood transfusion is considered for surgical patients. Third, sleep disturbance is common in patients admitted to ICU and is linked to functional disability after critical illness [42,43]. For patients at high risk of NPUSH, sleep medicine or psychiatric consultations may be required to improve postoperative sleep and to prevent sedative–hypnotic misuse. Future studies are warranted to evaluate the potential effect of modifiable disruptors to patient sleep in ICUs (e.g., noise, light, and patient care activities) on the long-term risk of sedative–hypnotic dependence and misuse [42].

There are some limitations to our study. First, our data did not contain information about objective physical measures (e.g., polysomnography parameters), biochemical laboratory tests (e.g., inflammation markers), the American Society of Anesthesiologists physical status, pain intensity, and clinical data on detailed surgical (e.g., elective, emergency, or urgent surgery, wound size, and operative duration) and anesthetic management (e.g., types and doses of opioids and non-opioid anesthetic drugs) that were not covered by the NHI research database. Second, it is possible that anesthesiologists may have chosen to prescribe general anesthesia to patients with an undocumented and untreated history of general anxiety disorders or other borderline psychiatric conditions [44,45]. The psychological predisposition and undiagnosed anxiety disorder could not be adjusted for in the multivariable analyses due to the lack of relevant data. In addition, although we did not consider the use of anxiolytics in the patient selection, the included benzodiazepine drugs are commonly used as preoperative anxiolytics [46]. Third, the indications for postoperative sedative–hypnotic prescriptions were unknown in some patients. Therefore, the biological mechanism of anesthesia-related NPUSH remains to be investigated. Fourth, we did not evaluate the sedative–hypnotic use beyond 180 days after surgery. It is uncertain whether the NPUSH developed into a long-term dependence or misuse. Fifth, this study did not include patients receiving peripheral nerve blocks due to its small patient sample and analytical difficulty in matching three groups. Last, our cohort was only followed up until December 31, 2013, due to the regulations of the NHI research database.

5. Conclusions

Patients undergoing general anesthesia had an increased risk of NPUSH and sleep disorders compared with neuraxial anesthesia among surgical patients. The general-anesthesia-related NPUSH risk persisted 90 to 180 days after surgery. More studies are needed to clarify the potential causal relationship and biological mechanism, and to evaluate the potential impact on anesthesia care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11123360/s1, Table S1. ICD-9-CM codes of coexisting diseases, lifestyle factors, postoperative complications, and outcomes.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the regulations of the Institutional Review Board.

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