Sex-related differences in postoperative complications following elective craniotomy for intracranial lesions
An observational study

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Abstract

Introduction: The integration of sex-related differences in neurosurgery is crucial for new, possible sex-specific, therapeutic approaches. In neurosurgical emergencies, such as traumatic brain injury and aneurysmal subarachnoid hemorrhage, these differences have been investigated. So far, little is known concerning the impact of sex on frequency of postoperative complications after elective craniotomy. This study investigates whether sex-related differences exist in frequency of postoperative complications in patients who underwent elective craniotomy for intracranial lesion.

Material and Methods: All consecutive patients who underwent an elective intracranial procedure over a 2-year period at our center were eligible for inclusion in this retrospective study. Demographic data, comorbidities, frequency of postoperative complications at 24 hours following surgery and at discharge, and hospital length of stay were compared among females and males.

Results: Overall, 664 patients were considered for the analysis. Of those, 339 (50.2%) were females. Demographic data were comparable among females and males. More females than males suffered from allergic, muscular, and rheumatic disorders. No differences in frequency of postoperative complications at 24 hours after surgery and at discharge were observed among females and males. Similarly, the hospital length of stay was comparable.

Conclusions: In the present study, no sex-related differences in frequency of early postoperative complications and at discharge following elective craniotomy for intracranial lesions were observed.

Abbreviations: ACS = acute coronary syndrome, ASA = American Society of Anesthesiology, ICU = intensive care unit, LOS = length of stay.

Key Words: gender medicine, neurosurgery, surgical complications, intracranial tumors, intensive care unit

1. Introduction

Sex-related differences regarding patients’ characteristics at hospital admission, provided care, and outcomes have been extensively studied within the field of cardiology[1–3] and critical care.[4,5] In the context of neurosurgery, the impact of sex is less investigated. While some data in patients following neurosurgical emergencies, such as after traumatic brain injury and aneurysmal subarachnoid hemorrhage, are available, [6–4] in patients admitted for elective neurosurgical procedures the evidence on the impact of sex is scarce. In patients who underwent elective lumbar spine surgery, sex-related differences in preoperative disabilities[8–11] hospital length of stay (LOS),[14] and postoperative satisfaction[15] were found. Indeed, in patients who underwent elective neurosurgery for intracranial lesions, only few studies in patients with glioblastoma,[16–18] meningioma,[19] and pituitary macroadenomas[20] specifically investigated sex-associated differences preoperatively and on outcomes. Most of the available studies investigated the impact of sex on mortality. However, sex-related differences in frequency of postoperative complications are rarely investigated and systematically collected.

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The integration of sex-related differences in health care is crucial to bring insight for new, and possible sex-specific, therapeutic approaches, including in neurosurgery. In patients with acute coronary syndrome, for example, sex-differences in symptom presentation are well-established, so that the terms “atypical” and “typical” to label symptoms of acute coronary syndrome are now outdated.[3]

The present retrospective study investigates whether sex-related differences exist in frequency of postoperative complications in patients who underwent elective intracranial procedures for intracranial lesion. A better understanding of predictors of postoperative complications may allow clinicians to more accurately advise patients on the risks and benefits of undergoing neurosurgical procedure, as well as adapt postoperative care to patient need.

2. Materials and Methods
All patients who underwent elective resection or biopsy for a suspected intracranial lesion between June 2015 and May 2017 at
our hospital were eligible for inclusion in this retrospective observational study. Inclusion criteria were as follows: (1) adults (>18 years aged), (2) presence of an intracranial lesion, (3) elective craniotherapy, (4) postoperative admission at the ICU. Exclusion criteria was written or documented oral refusal of the patient to have his data analyzed for research projects. Primary endpoint was a difference in frequency of postoperative complications within 24 hours after surgery and during the hospital stay among women and men.

The local ethic committee approved the study. STROBE guidelines were employed to draft the manuscript. Data were obtained from our institutional ongoing prospective patient registry. Demographic data collected included: sex, age, comorbidities, smoking, or alcohol abuse. Comorbidities were assessed by the preoperative anesthesiology evaluation, and they were organ-specifically collected. Preoperative laboratory values were evaluated in a binary way (yes/no) and included electrolyte disorders of sodium or potassium, coagulation test disorders (prolonged prothrombin time, reduced platelets count), hepatic or renal disorders (increased transaminases, decreased glomerular filtration rate below 60 ml/min), and cardiac disorders (increased cardiac markers as troponin and myoglobin). Furthermore, at hospital admission, the following scores were determined and collected: Karnofsky Performance Scale and the American Society of Anesthesiology classification. The histological nature of the intracranial lesion was collected. Primary outcome was the occurrence of a postoperative complication within the first 24 hours as well as until discharge. Complications were defined as any deviation from expected postoperative course and classified according to the Clavien-Dindo-classification (Table 1). [22]

### Table 3
#### List of postoperative complications

| Complication                                      | N (%) | P  |
|---------------------------------------------------|-------|----|
| None                                              | 440 (67.2) |    |
| New neurological deficit (including transient)    | 101 (15.1) |    |
| Seizures                                          | 17 (2.5) |    |
| Delayed awakening                                 | 21 (3.1) |    |
| Postoperative bleeding                            | 10 (1.5) |    |
| Intraoperative bleeding                           | 4 (0.6)  |    |
| Others                                            | 19 (2.8)  |    |
| Metabolic                                          | 12 (1.8)  |    |
| Urinary tract infection                           | 7 (1.0)  |    |
| Delirium                                          | 6 (0.9)  |    |
| Cerebral infarction                               | 6 (0.9)  |    |
| Thromboembolic complication                       | 6 (0.9)  |    |
| CSF fistula                                       | 4 (0.6)  |    |
| Postoperative bleeding                            | 4 (0.6)  |    |
| Intraoperative bleeding                           | 4 (0.6)  |    |
| Others                                            | 19 (2.8)  |    |
| Urinary tract infection                           | 6 (0.9)  |    |
| Metabolic                                          | 12 (1.8)  |    |
| Intraoperative bleeding                           | 4 (0.6)  |    |
| Others                                            | 19 (2.8)  |    |

Data are presented in frequency (percentage). CSF = cerebrospinal fluid.

### Table 4
#### Frequency of complications at discharge and at 24 hours following intracranial surgery, and hospital length of stay in the study population

| Outcome                          | Overall (N/%) | Male (N/%) | Female (N/%) | P  |
|----------------------------------|---------------|------------|--------------|----|
| **Complication at discharge**    |               |            |              |    |
| CDG N = 663                      | 184/664 (27.7)| 87/325 (26.8)| 97/339 (28.6)| .61|
| 0                                | 448 (67.5)    | 222 (68.6) | 226 (66.7)   | .70|
| 1                                | 128 (19.3)    | 62 (19.1)  | 66 (19.5)    |    |
| 2                                | 60 (9.0)      | 26 (8.0)   | 34 (10.0)    |    |
| 3                                | 4 (0.6)       | 2 (0.6)    | 2 (0.6)      |    |
| 3a                               | 3 (0.9)       | 1 (0.3)    | 2 (0.6)      |    |
| 3b                               | 12 (1.8)      | 7 (2.2)    | 5 (1.5)      |    |
| 4                                | 1 (0.2)       | 1 (0.3)    |             |    |
| 4a                               | 6 (0.9)       | 3 (0.9)    | 3 (0.9)      |    |
| 5                                | 1 (0.2)       |            | 1 (0.3)      |    |
| **Complication at 24 h**         |               |            |              |    |
| CDG N = 663                      | 171/663 (25.8)| 84/325 (25.8)| 87/338 (25.7)| 1 |
| 0                                | 490 (73.9)    | 241 (74.2) | 249 (73.7)   | .97|
| 1                                | 138 (20.8)    | 64 (19.7)  | 74 (21.9)    |    |
| 2                                | 31 (4.7)      | 17 (5.2)   | 14 (4.1)     |    |
| 3b                               | 4 (0.6)       | 3 (0.9)    | 1 (0.3)      |    |

Data are expressed as frequency and percentage or mean and standard deviation. CDC = Clavien-Dindo Classification; hospital LOS = hospital length of stay.
our patients' sample can be expected to reflect true incidence in ing patients referral system in Switzerland, data resulting from on the contrary, were found more often in men. Given the exist-

Therefore, postoperative complications were not collected prospectively and systematically with a recognized score such as the Clavien-Dindo classification, which has been validated for multiple neurological conditions.

Finally, comorbidities were not summarized organ-specifically, as we did. Our approach thus reduces the risk of underestimation of the real frequency of postoperative complications and comorbidities.

As possible explication of the lack of any sex-associated differences in postoperative complications following elective craniotomy, we postulate that the role of sex hormones might differ in critical settings as compared to elective surgery. Accordingly, it has been shown, that men and women react differently to stress-induced increased cortisol levels, as might be the case in emergencies. Furthermore, previously reported sociodemographic aspects and gender-bias favorable for males influencing treatment decisions and care delivery might be less pronounced in elective settings. Finally, it is also possible that gender-bias are less disseminated in the medical personnel of our institution than in others, thus resulting in the findings presented in this study.

Even if this is a “negative” study, it suggests that in the setting of elective neurosurgery for intracranial lesions sex-related differences seem to be less evident than in other medical fields.

There are several limitations to this study. First, this is the experience of a single-center, limiting the generalizability of our findings. There are some evidence the also geographical aspects might play a role in frequency of sex-related differences in delivery of care. Second, the results presented here may remain residually confounded by unmeasured factors associated with both sex and outcomes of interest. Third, we limited our analysis to early complications after surgery, further prospective studies with larger numbers and longer follow-up are required to investigate the long-term outcome. Fourth, we limited our analysis to patients admitted postoperative at the ICU. If the study had also taken into consideration patients admitted to the intermediate care unit or the neurosurgical ward, the results would probably have been different. Finally, the small sample size is a further limitation of the study.

The role of sex and gender on frequency of postoperative complications in patients undergoing elective neurosurgery for intracranial lesions is complex and is likely to be multifactorial, involving sociocultural, hormonal, and disease-specific aspects. Contrarily to previous reports, we did not observe any significant sex-related difference in the occurrence of postoperative complications, either in the short-term (<24 hours) or at the whole population. These results support that sex-differences in brain cancer exist. This might be attributed to the difference in molecular, genetic, hormonal and evolutionary biology of both sexes. Despite the small number of patients per type of intracranial lesion in the study population, these results confirm and correspond to previous epidemiological reports.

In case of emergencies, sex-related discrepancies in patients’ characteristics, provided care, and outcomes in many fields of health care have been reported. Similarly, in neurosurgical emergency patients, sex-related discrepancies are reported. In case of elective intracranial surgery, on the contrary, data concerning these sex-related differences are scarce, with some exceptions, such as in patients with glioblastoma or meningioma.

So far, very little is known about the frequency of short-term complications following elective craniotomy. In a previous investigation on the relationship between sex and postoperative complications after neurosurgery, male sex was associated with higher risk of postoperative complications as well as longer hospital stay. Our findings do not confirm that men fare worse than women do. However, in the previous report, both craniotomy and spinal cases were included in the analysis, while our study focuses on patients following craniotomy only. Furthermore, postoperative complications were not collected prospectively and systematically with a recognized score such as the Clavien-Dindo classification, which has been validated for multiple neurological conditions.

Finally, comorbidities were not summarized organ-specifically, as we did. Our approach thus reduces the risk of underestimation of the real frequency of postoperative complications and comorbidities.

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discharge. This study gives more insight on the impact of sex on frequency of short-term complications following elective craniotomy and contributes to improve the use of resources and delivery of care.

Author contributions

Study conception and design: GB, SW, CS, EK, LR
Material preparation, data collection and analysis: GB, VS, MG, LT, JS, SW, BVN
Writing the first draft of the manuscript: GB, VS
Approval of the final manuscript: all authors.

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