Observational Study

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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, [6–8] 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[9–13] 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.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1

Grading of the postoperative complications based on the Clavien-Dindo-Classification.

Grade I	Any deviation from the normal postoperative course not requiring surgical, endoscopic or radiological intervention; this includes certain drugs (e.g., antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside.
Grade II	Complications requiring drug treatments other than those allowed for Grade I complications; these include blood transfusion and TPN.
Grade III	Complications requiring surgical, endoscopic or radiological intervention.
Grade IIIa	Intervention not under general anesthetic.
Grade IIIb	Intervention under general anesthetic.
Grade IV	Life-threatening complications; these include CNS complications (e.g., brain hemorrhage, ischemic stroke, subarachnoid hemorrhage) which require intensive care, but excludes TIAs.
Grade IVa	Single-organ dysfunction (including dialysis).
Grade IVb	Multiorgan dysfunction.
Grade V	Death of the patient.

CNS = central nervous system, TIA = transient ischemic attacks, TPN = total parenteral nutrition.

Table 2

Demographic data, clinical scores, and comorbidities of the study population

Demographic	Overall	Male	Female	*P*
Sex	664	325(48.9)	339(51.1)	
		Mean (SD)	**Mean (SD)**	
Age	56.56 (15.79)	57.19 (15.44)	55.95 (16.11)	.31
BMI (kg/m^2)	25.86 (5.42)	26.43 (4.83)	25.33 (5.88)	<.05
Smoking status	N = 658	N = 323	N = 335	<.05
No	378 (57.4)	165 (51.1)	213 (63.6)	
Stopped	132 (20.1)	76 (23.5)	56 (16.7)	
Yes	148 (22.5)	82 (25.4)	66 (19.7)	
Alcohol abuse	31/657 (4.7)	21/323 (6.5)	10/334 (3.0)	<.05
Clinical scores				
ASA class	N = 633	N = 311	N = 322	<.05
1	43 (6.8)	20 (6.4)	23 (7.1)	
2	350 (55.3)	159 (51.1)	191 (59.3)	
3	224 (35.4)	123 (39.5)	101 (31.4)	
4	16 (2.5)	9 (3.0)	7 (2.2)	
Risk class	N = 589	N = 288	N = 301	.28
1	2 (0.3)	1 (0.3)	1 (0.3)	
2	2 (0.3)	-	2 (0.7)	
3	135 (22.9)	72 (25.0)	63 (20.9)	
4	450 (76.4)	215 (74.7)	235 (78.1)	
KPS at admission	82.42 (15.61)	82.89 (15.78)	81.96 (15.46)	.31
Comorbidites				
Cardiac disorder	166/623 (26.6)	86/307 (28.0)	80/316 (25.3)	.47
Vascular disorder	60/625 (9.6)	29/309 (9.4)	31/316 (9.8)	.89
Hematologic disorder	40/623 (6.4)	15/308 (4.9)	25/315 (7.9)	.13
Respiratory disorder	76/627 (12.1)	39/309 (12.6)	37/318 (11.6)	.72
Hepatic disorder	20/625 (3.2)	13/306 (4.2)	7/319 (2.2)	.17
Renal disorder	28/624 (4.5)	17/306 (5.6)	11/318 (3.5)	.24
Metabolic disorder	98/627 (15.6)	49/308 (15.9)	49/319 (15.4)	.91
Allergic disorder	155/624 (24.8)	52/307 (16.9)	103/317 (32.5)	<.001
Neurological disorder	216/621 (34.8)	97/303 (32.0)	119/318 (37.4)	.18
Gastrointestinal disorder	93/627 (14.8)	45/309 (14.6)	48/318 (15.1)	.91
Skeletal disorder	110/621 (17.7)	52/308 (16.9)	58/313 (18.5)	.60
Muscular/rheumatic disorder	31/621 (5.0)	7/307 (2.3)	24/314 (7.6)	<.01
Ophthalmologic disorder	99/611 (16.2)	42/301 (14.0)	57/310 (18.4)	.15
Odontoiatric disorder	123/606 (20.3)	59/310 (19.0)	64/296 (20.6)	.85
Previous anesthesia problems	23/565 (4.1)	5/284 (1.8)	18/281 (6.4)	<.01

Data are expressed as frequency with (percentage) or mean with (standard deviation), as indicated. A comparison between male and female was performed.
ASA = Class American Society of Anesthesiologist Classification, BMI = body mass index, KPS = Karnofsky performance status scale.

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

Table 3

List of postoperative complications

Complication	N (%)
None	449 (67.2)
New neurological deficit (including transient)	101 (15.1)
Seizures	17 (2.5)
Delayed awakening	21 (3.1)
Postoperative bleeding	16 (2.4)
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)
Intraoperative bleeding	4 (0.6)
Others	19 (2.8)

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

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 craniotomy, (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. [21] Demographic data collected included: sex, age, comorbidities, smoking, or alcohol abuse. Comorbidities were assessed by the preoperative anesthesia 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]

2.1. Statistical analysis

We tested associations between sex and covariates using the Chi-squared test for categorical variables, Student's t-test for continuous variables and Wilcoxon Mann-Whitney test for ordinal variables. Similar analyses were performed for the outcome and occurrence of any in-hospital complications.

Missing data were excluded for statistical analysis. All analyses were performed with *R* Version 3.5.3 (The *R* Foundation for Statistical Computing).

3. Results

Overall, 664 patients underwent elective surgery for intracranial lesions in the study period and were included in the analysis. Of those, 339 (51.1%) were females. Demographic data, scores at admission, and comorbidities were similar among females and males (Table 2). Females presented more often allergic ($P < .001$) and muscular/rheumatologic diseases ($P < .01$) then males. Concerning preoperative laboratory values, no differences were found among females and males with the exception of the hemoglobin values, which were significantly lower in females (data not shown). The most frequent complications observed are listed in Table 3. No differences in frequency of postoperative complications among females and males were observed both within 24 hours after surgery ($P = 1$) and during the whole hospitalization ($P = .70$), as shown in Table 4. Hospital LOS was also similar among females and males ($P = .15$), as presented in Table 4.

The histological diagnoses of the intracranial lesions are listed in Table 5. Meningiomas were significantly more frequent in females than in males ($P < .001$). Glioblastomas, on the contrary, were significantly more frequent in males ($P < .001$).

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	184/664 (27.7)	87/325 (26.8)	97/339 (28.6)	.61
CDG	N = 663	N = 324	N = 339	.70
0	448 (67.5)	222 (68.6)	226 (66.7)	
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 (0.5)	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	171/663 (25.8)	84/325 (25.8)	87/338 (25.7)	1
CDG	N = 663	N = 325	N = 338	.97
0	490 (73.9)	241 (74.2)	249 (73.7)	
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)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Hospital LOS (days)	9.7 (±6.1)	9.8 (±6.8)	9.6 (±5.3)	.15

Data are expressed as frequency and percentage or mean and standard deviation.
CDC = Clavien-Dindo Classification, hospital LOS = hospital length of stay.

Table 5

Histology stratification by gender

Histology		*P*
Gliomas		
Glioblastoma		
Total	134/664 (20.2)	
Male	86/325 (26.5)	<.001
Female	48/339 (14.2)	
Astrocytoma grade II and III		
Total	47/664 (7.1)	
Male	29/325 (12.0)	.09
Female	18/339 (5.3)	
Astrocytoma grade I		
Total	7/664 (1.0)	
Male	3/325 (0.9)	1
Female	4/339 (1.2)	
Oligodendroglioma		
Total	35/664 (5.3)	
Male	17/325 (5.2)	1
Female	18/339 (5.3)	
Meningioma		
Total	147/664 (22.1)	
Male	44/325 (13.5)	<.001
Female	103/339 (30.4)	
Grade I		
Total	116/664 (17.5)	
Male	31/325 (9.5)	<.001
Female	85/339 (25.1)	
Grade II, III		
Total	31/664 (4.6)	
Male	13/325 (4.0)	.46
Female	18/339 (5.3)	
Pituitary adenoma		
Total	63/664 (9.5)	
Male	29/325 (8.9)	.70
Female	34/339 (9.7)	
Metastases		
Total	110/664 (16.6)	
Male	56/325 (17.2)	.68
Female	54/339 (15.9)	
Lymphoma		
Total	16/664 (2.4)	
Male	8/325 (2.5)	1
Female	8/339 (2.4)	
Schwannoma		
Total	22/664 (3.3)	
Male	10/325 (3.1)	.83
Female	12/339 (3.5)	
Others		
Total	83/664 (12.5)	
Male	43/325 (13.2)	.63
Female	40/339 (11.8)	

4. Discussion

In our cohort of 664 consecutive patients following elective surgery for intracranial lesions, we found no sex-related differences in frequency of complications during the hospitalization.

Demographic data, comorbidities, scores at admission, and hospital LOS were not different between males and females. Only allergies and muscular and rheumatic disorders were more frequent in females, as in previous reports. [23–25] Furthermore, males had a trend for more alcohol dependence, as previously reported in other settings than elective neurosurgery. [26]

Concerning the histological nature of the intracranial lesions, meningioma was the most frequent diagnosis and occurred with a striking sex disparity. Meningiomas, in fact, occurred more than twice in females, as previous reported. [27] Glioblastomas, on the contrary, were found more often in men. Given the existing patients referral system in Switzerland, data resulting from our patients' sample can be expected to reflect true incidence in 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. [27] Despite the small number of patients per type of intracranial lesion in the study population, these results confirm and correspond to previous epidemiological reports. [28–30]

In case of emergencies, sex-related discrepancies in patients' characteristics, provided care, and outcomes in many fields of health care have been reported. [2,31–33] Similarly, in neurosurgical emergency patients, sex-related discrepancies are reported. [34,35,36] 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.[16–19]

So far, very little is known about the frequency of short-term complications following elective craniotomy.[37,38] 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. [37] 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 neurosurgical conditions. [39–42]

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,[43,44] as might be the case in emergencies. Furthermore, previously reported sociodemographic aspects[4] and gender-bias favorable for males influencing treatment decisions and care delivery [4,45,46] 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.[47] 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

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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