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RESEARCH ARTICLE

Rate of Postoperative COVID-19 Infection After Endonasal Transsphenoidal Surgery and Evaluation of Factors Affecting COVID-19 Transmission

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ABSTRACT

Objective: Endonasal transsphenoidal surgery (ETS) is considered to be among the high-risk procedures for coronavirus disease 2019 (COVID-19) exposure. This study aimed to investigate postoperative COVID-19 infection rate and mortality in patients undergoing ETS and contribute to the literature by establishing the factors causing viral transmission.

Materials and Methods: This single-center, retrospective cohort study included patients who underwent surgery between July 2020 and March 2021. Data comprised the patients' demographic, preoperative, intraoperative, and postoperative characteristics and their postoperative COVID-19 infection and mortality rates.

Results: We included 37 patients with a mean age of 51.32±13.55 years and a female-to-male ratio of 15:22. Further, 26 (70.30%) of 37 patients had non-functioning pituitary adenoma, 6 (16.20%) had acromegaly, 2 (5.40%) had Cushing's disease, 2 (5.40%) had meningioma, and 1 (2.70%) had chordoma. The mean duration of postoperative follow-up was 5.58±2.27 (2–10 months). The COVID-19 infection rate was 13.50% (5/37), and the mortality rate was 2.70% (1/37). There was no significant difference between postoperative COVID-19-positive and COVID-19-negative patients regarding age, gender, comorbidities, length of hospital stay, pathology type, diaphragma sellae injury, use of high-speed drill, and hormone insufficiency (p>0.05).

Conclusion: This study demonstrated no effect of ETS on COVID-19 transmission risk in health-care staff and patients if appropriate measures recommended in the guidelines are followed. We believe that pre-existing comorbidities or post-operative complications pose the highest COVID-19 transmission risk in pituitary adenoma patients; however, appropriate management can minimize the transmission rates.

Keywords: COVID-19, endoscopic transsphenoidal surgery, pituitary adenoma

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 that was detected in Wuhan, China, in December 2019.[1] COVID-19 rapidly spread worldwide and was declared a pandemic by the World Health Organization on March 11, 2020.[2]

In neurosurgery, patients with sellar pathologies, particularly pituitary adenomas, are one of the most affected patient groups by the pandemic.

In a report published by Zhu et al.[3] at the beginning of the COVID-19 pandemic, one patient undergoing endonasal transsphenoidal surgery (ETS) due to pituitary adenoma developed COVID-19 symptoms in the postoperative period and died 1 month after. Four HCWs in contact with the patient and 10 HCWs without a contact history were later diagnosed with COVID-19. It was stated that ETS procedures must be suspended except in emergencies and that personal protective equipment (PEE) should be used if the procedure cannot be postponed. The guidelines published by the pituitary society

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recommended proceeding with surgery in patients with pituitary apoplexy, acute or progressive loss of vision, malignant pathologies, and those without a definitive diagnosis and rescheduling patients with asymptomatic tumors as elective cases. Furthermore, PPE was recommended in all cases.[4]

Limited data are available in the literature regarding the effect of pre-existing comorbidities of patients with pituitary adenoma and hormonal complications that may occur postoperatively on the risk of COVID-19 transmission.

The present study aims to share our experience with patients who were operated on using the ETS method during the pandemic, investigate postoperative COVID-19 positivity and associated mortality rates, and contribute to the literature by identifying the factors that might have caused disease transmission.

MATERIALS and METHODS

This study included patients who underwent ETS in our neurosurgery clinic. The study was designed as a retrospective cohort study. The study was initiated after obtaining approval from the hospital's ethics committee. The study data were reviewed retrospectively from the patients' medical charts. An inquiry was made into the patient's medical records for postoperative COVID-19 positivity and the date the patient had suffered from COVID-19 (https://lbys.saglik.gov.tr/). In addition, all patients were contacted by phone to inquire about COVID-19 transmission, close contact with a COVID-19 patient, and the occurrence of symptoms and their responses were recorded.

Patient Selection

The study included 37 patients who underwent surgery between July 02, 2020, and March 15, 2021. The decision of surgery on patients with pituitary adenoma was made by a joint council involving endocrinologists. Patients with a postoperative follow-up duration of fewer than 2 months were excluded from the study. In addition, the decision for surgery was made in symptomatic patients, patients with macroadenomas, and those with neurological deficits. None of the patients received a COVID-19 vaccine in the preoperative period.

Preoperative Evaluation

Nasopharyngeal swab specimens were tested by the quantitative reverse-transcriptase polymerase chain reaction (RT-qPCR) to identify COVID-19 positivity. RT-qPCR test was performed at most 1 day before surgery. Asymptomatic patients with a positive RT-qPCR test underwent surgery after the completion of the COVID-19 therapy and observed two subsequent negative results on RT-qPCR.

Perioperative Management

The surgical team comprised two neurosurgeons, two nurses, one anesthesiologist, one anesthesiology technician, and one operating room technician. As a standard, the surgical team wore a surgical cap, a surgical mask on top of an N95 mask, a waterproof apron, and a pair of gloves. Few members of the surgical team optionally used a face shield and double-gloving. The surgical team members were kept outside of the operating room during intubation.

Postoperative Evaluation

Patients undergoing the standard endoscopic technique were transferred to the ward after surgery. Patients undergoing surgery using the extended approach remained in the intensive care unit for 1 day for follow-up before being transferred to the regular ward. The nasal packs were removed on day two in patients with nasal packing. Patients without overt hormone insufficiency, DI, or rhinorrhea were discharged from the hospital. The patients were warned about COVID-19 symptoms and postoperative complications. They were advised to self-isolate for 15 days after discharge and use face masks. The patients attended control visits at 15 days, 1 month, and 3 months after surgery.

Statistical Analysis

The compatibility of the data to the normal distribution was examined by the Shapiro-Wilk test. The continuous variables are expressed with mean±standard deviation and median (interquartile range) values, whereas categorical variables are given with frequency and the corresponding percentage value. The Mann-Whitney U test, Fisher's exact test, and Fisher-Freeman-Halton tests were used to compare postoperative COVID positive and negative cases. In statistical comparisons, SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) software package was used for the statistical analysis. The type I error level was accepted as 5%.

RESULTS

Patient Demographics

The study included 37 patients. The mean age was 51.32±13.55 (range 26–30) years. The female-to-male ratio was 15:22, and the rate of comorbidities was 51.40% (18/37). The demographic characteristics of the patients are summarized in Table 1.

Preoperative Characteristics of Patients

The loss of vision ranked first among the presenting symptoms, whereas 15 patients had a headache, and six patients

Table 1. Demographic characteristics of the patients

	n=37	
	n	%
Age (years)	51.32±13.55 (26–80)	
Gender		
Female	15	
Male	22	
Comorbidity	18	51.40
HT	17	45.90
DM	6	16.20
Other	2	5.40

Data are presented as mean±standard deviation (minimum:maximum) and n, %. HT: Hypertension; DM:Diabetes mellitus

had soft tissue swelling and joint pain on admission. Of 37 patients, 34 had pituitary adenoma, 2 had meningioma, and 1 had chordoma. Of the patients, 26 had non-functioning pituitary adenoma (NFPA), 6 had acromegaly, and 2 had Cushing's disease (CD). Thirteen patients had preoperative hormone insufficiency. All patients had hypocortisolism, and two patients had accompanying hypogonadism. Two asymptomatic patients with NFPA and CD tested positive for COVID-19 on an RT-qPCR test. Preoperative hospital length of stay ranged from 1 to 4 days. The preoperative characteristics of the patients are summarized in Table 2.

Operation Characteristics

The standard approach was used in 32 and the extended approach was used in 5 patients. Eleven patients underwent surgery using the bi-nostril approach and 22 using the mono-nostril approach. Surgical cautery was used in all patients, and a high-speed micro-drill was used in 28 patients. An injury to the diaphragma sellae was detected in four patients undergoing surgery using the extended approach and 12 patients using the standard procedure. In addition, bi-nostril nasal packing was performed in 16 patients. The operative data of the patients are summarized in Figure 1.

Postoperative Follow-up and Complications

Nasal packs were left in place for 2 days. Two patients had temporary and two patients had permanent DI. Desmopressin therapy was initiated in patients with permanent DI. Three patients developed recent-onset hormone insufficiency after surgery. None of the patients developed rhinorrhea. The remaining patients showed no symptoms associated with COVID-19. The mean length of hospital stay after surgery was 5.58±2.27 days (3–25). The total number

Table 2. Preoperative data

	n=37	
	n	%
Presenting symptoms		
Loss of vision	16	43.20
Headache	15	40.50
Soft-tissue swelling	6	13.20
Pathology		
NFPA	26	70.30
GH Adenomo	6	16.20
CD	2	5.40
Meningioma	2	5.40
Chordoma	1	2.70
Adenoma size (n=34)		
Giant	29	78.40
Macro	4	10.80
Micro	1	2.70
Hormone insufficiency	13	35.10
Preoperative positive PCR for COVID-19	2	5.40
Number of PCR tests	1 (1) 1.89±1.37	
Length of hospital stay (day)	2 (1) 1.81±0.97	

Data are presented as median (interquartile range), mean±standard deviation and n, %. NFPA: Non Functional Pituitary Adenoma; CD: Cushing's disease

of patients with hormone insufficiency was 16 (13 before surgery, three after surgery). Postoperative data of the patients are summarized in Table 3.

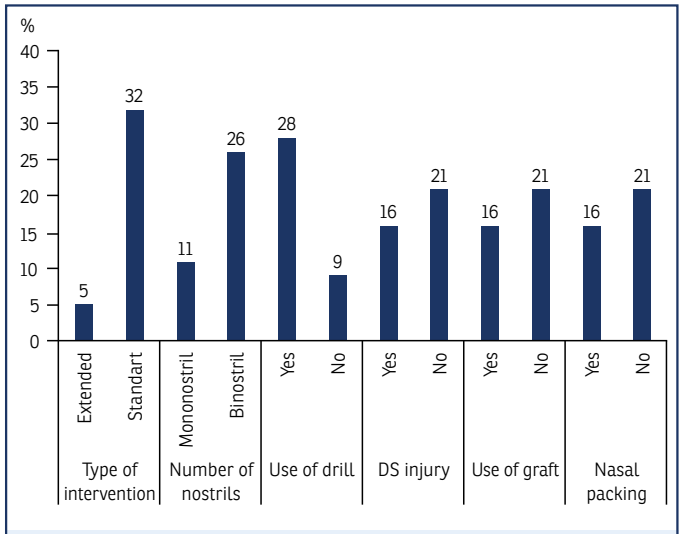

Figure 1. Operative data

DS: Diaphragma sellae

Table 3. Postoperative data

	n=37	
	n	%
Duration of follow-up (month)	5.58±2.27 (2:10)	
Hormone insufficiency	16	43.20
Diabetes insipidus	4	10.80
Length of hospital stay (day)	6 (2.50) 6.65±3.56	
Postoperative COVID-19	5	13.50

Data are presented mean±standard deviation (minimum:maximum) and n, %

Postoperative COVID-19 Screening

A total of 5 patients (13.5%), including three patients with NFPA, 1 with acromegaly, and 1 with CD, suffered from COVID-19 in the postoperative period. The onset of COVID-19 was 1–7 months after surgery. One patient died, and the remaining patients recovered without sequelae. There was no significant difference between postoperative COVID-19-positive and COVID-19-negative patients in terms of age, gender, comorbidities, the total length of hospital stay, type of pathology, type of intervention, number of nostrils, use of the high-speed drill, diaphragma sellae injury, use of nasal packs, hormone insufficiency, and DI (p>0.05). The statistical analysis of factors that may affect postoperative COVID-19 transmission is summarized in Table 4.

Table 4. COVID-19 transmission after ETS

	Postoperative COVID-19				p
	Positive (n=5)		Negative (n=32)		
	n	%	n	%	
Total length of hospital stay (day)	7 (1.50) 6.80±0.84		8 (2.75) 8.72±4.20		0.140*
Surgery time (minutes)	185 (35) 195±11.4		177.5 (58.75) 187.25±11.58		0.286*
Age	58 (31.5) 52.6±7.48		54.5 (25.25) 51.09±2.56		0.773*
Pathology					
NFPA	3	60	23	71.90	
GH Adenoma	1	20	5	15.60	
CD	1	20	1	3.10	0.544†
Meningioma	0	0	2	6.30	
Chordoma	0	0	1	3.10	
Type of Intervention					
Extended	0	0	5	15.60	>0.99‡
Standard	5	100	27	84.40	
Number of nostrils					
Monostril	3	60	8	25	0.144‡
Binostril	2	40	24	75	
Use of drill	4	80	24	75	>0.99‡
Injury to the DS	1	20	15	46.90	0.364‡
Nasal Packing	1	20	15	46.90	0.364‡
Hormone Insufficiency	1	20	15	46.90	0.364‡
Diabetes Insipidus	0	0	4	12.50	>0.99‡

Data are presented as median (interquartile range), mean±standard deviation, and n, %. *: Mann-Whitney U Test; †: Fisher-Freeman-Halton Test; ‡: Fisher's Exact Test. ETS: Endonasal transsphenoidal surgery; NFPA: Non Functional Pituitary Adenoma; CD: Cushing's disease; DS: Diaphragma sellae

DISCUSSION

ETS procedures have been resumed with a decrease in the number of COVID-19 cases and widespread and rapid use of RT-qPCR tests, and a limited number of case series and case reports have been published in the literature.

No viral transmission to the patients and surgical team has been reported in nine cases from Cambridge, United Kingdom.[5] Soliman et al.[6] reported no disease transmission in 16 patients, although one surgeon exhibited the symptoms despite a negative PCR test for COVID-19. Finally, in a series of three patients published in the early periods of the pandemic, Penner et al.[7] reported no disease transmission in any patient or the members of the surgical team.

In a prospective, observational cohort study with the participation of 12 centers in the United Kingdom and Ireland, no COVID-19 was detected in the HCWs or the patients up to 30 days after surgery in the 124 ETS procedures performed between March 23 and July 31.[8]

In our series, surgical cautery was used in all patients, and a high-speed drill was used in 28 patients. In addition, all surgical team members used PPE and no disease transmission to the personnel was found. This finding suggests that PCR-negative patients may be safe using a high-speed drill and a cautery device.

Young et al.[9] reported three cases with a negative preoperative PCR test which became COVID-19 positive in the early postoperative period after ETS. Pituitary insufficiency and surgical stress are the predisposing factors in contracting COVID-19, and the authors suggested that patients must be warned about this particular risk.

Five out of 37 patients in the present study tested positive for COVID-19 in the postoperative period. No statistically significant relationship was found between the risk of postoperative COVID-19 positivity and age, gender, comorbid conditions, the total length of hospital stay, type of pathology, type of intervention, number of nostrils, use of the high-speed drill, diaphragma sellae injury, use of nasal packs, hormone insufficiency, and DI.

Three patients with COVID-19 positivity in the postoperative period had NFPA, and these patients developed the disease at 1, 4, and 7 months after surgery. One patient developed COVID-19 1 week after her spouse tested positive for COVID-19. The other patients did not have a history of close contact with patients with COVID-19. The patient with acromegaly tested positive for COVID-19 2 months after surgery. All four patients completed their therapies at home without requiring hospitalization. These four patients did not develop hormone insufficiency, rhinorrhea, and DI before and after surgery. Considering the date these patients tested positive for COVID-19, it was evident that they did not contract the disease during the hospital stay.

Hyponatremia is a common finding in patients with COVID-19. Poor clinical outcomes and high mortality rates have been reported in patients with concurrent hyponatremia. In addition,[10] transient SIADH are among the postoperative complications that may cause hyponatremia. No COVID-19 transmission was detected in any of these patients. SIADH occurs 3–7 days after surgery and has a rate of approximately 4%–20%.[11] In our series, one patient developing SIADH 15 days after surgery was diagnosed with COVID-19 disease 10 days after discharge. Although the patient had a history of close contact with a patient with COVID-19, it was thought that the patient contracted the infection during the treatment of hyponatremia. The authors believe that the patients should be closely monitored for hyponatremia, and appropriate therapy should be initiated promptly while paying attention to the risk of COVID-19 transmission.

The authors would like to focus mainly on CD. Concerning the suppressive effect of hypercortisolism on the immune system, patients with CD are known to be more prone to bacterial, viral, and fungal infections than the average population.[12] In a recent study in the literature, the rate of COVID-19 was found to be higher in patients with CD than in the average population.[13] Belaya et al.[14] reporting on a series of three patients with CD, suggested a relationship between the severity of hypercortisolism and the severity of COVID-19 and stated that such patients require close follow-up to monitor for the development of COVID-19.

Unfortunately, we have had poor experiences with two patients in our case series who were operated on due to CD. The first patient had a severe clinical picture of CD, and the decision to perform surgery was made as the patient was refractory to medical therapy. However, the patient experienced a sudden change in his clinical condition in the early postoperative period. Initially, the patient was considered to have pulmonary thromboembolism and COVID-19; however, we failed to diagnose both conditions. The other patient contracted COVID-19 2 months after surgery. The interesting point in this patient was that she suffered from COVID-19 twice, only in a 3-month interval; she was asymptomatic during the first infection in the preoperative period, while the second infection after surgery resulted in death. The date of infection suggests that the virus has not been transmitted during her hospital stay. The patient did not suffer from rhinorrhea, DI, or surgical site infection in the postoperative period. She had high ACTH and mildly elevated prolactin levels before

surgery, and no hormone insufficiency was observed other than postoperative hypocortisolism, for which she received dexamethasone therapy. Although we could not provide evidence for an increased risk of COVID-19 transmission associated with ETS, we recommend avoiding surgery in patients with a CD, if possible, based on our experience with this case. The options of medical therapy and stereotactic radiosurgery must also be considered. Patients with CD are at high risk of contracting COVID-19 regardless of whether or not they have been operated on. Such patients must be provided with detailed information and monitored with close follow-up.

Although there is no publication in the literature regarding COVID-19 in patients with acromegaly, it was reported that particular attention should be paid to such patients as comorbidities, such as hypertension and hypoxemia associated with macroglossia, facilitate COVID-19 transmission.[15] Among these patients, only one tested positive for COVID-19 at postoperative 8 weeks; this patient was given appropriate therapy by the relevant department and recovered without requiring hospitalisation. Therefore, no finding in the present study suggested that ETS may facilitate COVID-19 transmission in patients with acromegaly.

CONCLUSION

The present study establishes the safety of performing ETS procedures using PPE. Although the present study has failed to provide solid evidence, we suggest that pre-existing comorbidities or postoperative complications are the essential factors for disease transmission in patients with pituitary adenoma. Therefore, properly managing such comorbidities can reduce transmission rates. We also believe that the intensity of patients with COVID-19 in a particular region should not be overlooked while deciding on surgery. Finally, we would like to emphasize the need for further studies to accumulate more data on the safety of HCWs and patients.

Disclosures

Ethics Committee Approval: The study was approved by the Bursa City Hospital Clinical Research Ethics Committee (No: 2020-8/4, Date: 07/10/2020).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

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