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# INCIDENCE AND PREDICTOR OF POSTOPERATIVE COGNITIVE DYSFUNCTION FOLLOWING PITUITARY ADENOMECTOMY: A PROSPECTIVE OBSERVATIONAL STUDY

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## Abstract

**Objective:** Postoperative cognitive dysfunction (POCD), particularly memory impairment, is a common complication following surgery and anesthesia. This study aimed to determine the incidence of POCD after pituitary adenoma excision surgery and to investigate the association between demographic characteristics and POCD.

**Methods:** Ninety-two ASA physical status II–III patients without neurological or psychiatric disorders scheduled for elective pituitary adenomectomy were enrolled after written informed consent was obtained from the patients or their legal representatives. Preoperative cognitive function was assessed using the Standardized Mini-Mental Test (SMMT) or the SMMT for Illiterate Individuals (SMMT-E). General anesthesia was induced with intravenous thiopental, remifentanil, and rocuronium and maintained with total intravenous anesthesia. Cognitive assessments were repeated at postoperative 1, 4, and 24 hours and 1 month. Statistical analyses included the Kolmogorov–Smirnov, Mann–Whitney U, and Kruskal–Wallis tests, with $p<0.05$ considered statistically significant.

**Results:** POCD was detected in 35.6%, 28.7%, 17.8%, and 11.7% of patients at the postoperative 1st hour, 4th hour, 24th hour, and 1 month, respectively. Total SMMT scores decreased significantly during the early postoperative period and returned to baseline by 1 month. Attention/calculation, recall, and language subscores were significantly lower at the 1st and 4th postoperative hours. Male patients had higher preoperative and early postoperative cognitive scores, whereas POCD occurred more frequently in female patients.

**Conclusion:** POCD frequently occurs during the first 24 hours after pituitary adenoma excision surgery, with cognitive function largely recovering by the first postoperative month.

**Keywords***: Postoperative Cognitive Dysfunction, Pituitary Adenoma Surgery, Neurocognitive Tests.*



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## Introduction

Major surgical procedures may lead to impairments in cognitive domains such as memory, attention, concentration, language, and social functioning,a condition defined as postoperative cognitive dysfunction (POCD). POCD can persist for weeks to months following surgery and may adversely affect patients quality of life. The clinical spectrum ranges from mild cognitive impairment to delirium and dementia.[1,2]

Anesthetic agents primarily exert their effects on the central nervous system and not only induce transient loss of consciousness but may also affect cognitive functions to varying degrees. Recovery of psychomotor and cognitive functions to preoperative levels after general anesthesia may be delayed; therefore, rapid and complete neurocognitive recovery is considered a key objective in anesthetic practice.[3]

The diagnosis of POCD is challenging due to the lack of specific clinical findings and the requirement to compare preoperative and postoperative cognitive status. It is generally based on measurable changes detected through neuropsychological testing.[3] The increasing elderly population and the growing emphasis on patient safety have heightened interest in POCD; nevertheless, its risk factors have not been fully elucidated. In this study, we aimed to determine the incidence of POCD and to investigate the effects of demographic characteristics on its development in patients undergoing pituitary adenoma excision using neuropsychological assessments.

## Methods

This study was conducted as a prospective, randomized controlled trial after obtaining approval from the Kocaeli University Faculty of Medicine Ethics Committee (GOKAEK 2017/153) and written informed consent from all participants. Between June 2017 and June 2018, a total of 92 patients aged 18–85 years, classified as ASA physical status II–III, and scheduled for elective pituitary adenomectomy by the Department of Neurosurgery were enrolled in the study.

Patients with significant cardiac, pulmonary, renal, or hepatic disease; a history of neurological disease, dementia, or psychiatric disorders, chronic drug or substance dependence, fluid–electrolyte imbalance, exposure to anesthesia within the previous 7 days, those undergoing emergency surgery, patients with visual, hearing, or communication impairments, patients who could not be extubated, required postoperative intensive care, had a Glasgow Coma Scale score below 15, experienced perioperative hemodynamic instability, or developed surgical complications, and those unwilling to participate were excluded from the study.

All patients were evaluated in the ward between 16:00 and 18:00 on the day before surgery. Demographic and clinical data including age, sex, marital status, level of education, place of residence, cohabitation status, history of surgery within the last six months, the primary caregiver, and whether the patient had undergone previous pituitary surgery were recorded. The Standardized Mini-Mental Test (SMMT) was administered. For illiterate patients, the Standardized Mini-Mental Test for Illiterate Individuals (SMMT-E) was used .[4] The SMMT consists of questions assessing orientation (first ten items), followed by registration memory, attention and calculation, recall, language function (including sentence construction), and visuomotor skills. The maximum total score is 30 points, and the test duration is approximately 10 minutes.

Based on these assessments, SMMT subgroup scores over time; SMMT scores according to sex, place of residence, history of surgery within the last six months, and history of previous pituitary surgery; percentage changes in total SMMT scores postoperatively; incidence of postoperative cognitive dysfunction (POCD) according to SMMT score distribution; and the relationships between operative duration and SMMT scores, POCD incidence and sex, and POCD and blood pressure values were evaluated.

Midazolam 2 mg was administered intravenously to patients in the preoperative waiting area for preoperative sedation. After transfer to the operating room, standard monitoring including electrocardiography, pulse oximetry, and invasive arterial blood pressure measurement was established. Following skin preparation of the frontal and temporal regions with alcohol, a Bispectral Index (BIS) sensor was applied. Prior to induction of anesthesia, patients were preoxygenated with 100% oxygen via a face mask for at least 3 minutes.

Anesthesia was induced with intravenous thiopental 5 mg/kg, remifentanil 1 µg/kg, and rocuronium 0.6 mg/kg, and tracheal intubation was performed 2 minutes later. Anesthesia was maintained using total intravenous anesthesia (TIVA) with a mixture of 40% $O_2$ and 60% air, along with propofol–remifentanil infusion. For maintenance, propofol infusion was initiated at 100 µg/kg/min and titrated to maintain a BIS value between 40 and 60, while remifentanil was administered at an infusion rate of 0.20 µg/kg/min. In cases of hypotension, an initial fluid bolus of 20 ml/kg was administered, followed by a 50% reduction in the remifentanil infusion rate if necessary. In the event of bradycardia, 0.5 mg atropine was administered intravenously. If the mean arterial pressure increased by more than 20%, the remifentanil infusion rate was increased.

Remifentanil infusion was discontinued 10 minutes before the end of surgery, followed by cessation of propofol. Neuromuscular blockade was reversed with 2 mg/kg sugammadex. Extubation criteria included the patient's ability to generate a tidal volume of 4–5 ml/kg and to maintain spontaneous breathing with room air without the oxygen saturation falling below 92%, which was set as the desaturation threshold.

In our study, the Aldrete scoring system was used to determine complete recovery, defined as the time when patients regained their preoperative systemic functions. The Aldrete score allows assessment not only of consciousness level but also of respiratory and circulatory system functions and muscle activity .[5] Aldrete recovery scores were calculated and recorded at the 15th minute after extubation. After extubation, once the patient was cooperative, a repeat SMMT assessment was attempted. Accordingly, the SMMT was reassessed at 1 hour, 4 hours, 24 hours, and 1 month postoperatively.

Postoperative analgesia was provided at the end of surgery with an intravenous infusion of 1 g paracetamol over 15 minutes. Analgesic maintenance in the neurosurgery ward was administered intravenously, twice daily, with 1 mg/kg tramadol. To prevent postoperative nausea and vomiting, intravenous ondansetron 0.15 mg/kg was administered.

**Statistical Analysis**

The data were analyzed using IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA). Normality of distribution was assessed with the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or median (25th–75th percentile), and categorical variables were expressed as frequency and percentage. Differences between

groups for non-normally distributed numerical variables were analyzed using the Mann–Whitney U test, Kruskal–Wallis one-way ANOVA, and Dunn's multiple comparison test. Differences between repeated measurements of non-normally distributed continuous variables were evaluated using Friedman ANOVA and Tukey's multiple comparison test. A p-value <0.05 was considered statistically significant for two-tailed tests.

The sample size for our study was calculated based on the study by Ucuzal and colleagues, titled "Postoperative Cognitive Changes in Elderly Patients," conducted in orthopedic, urology, and general surgery patient groups, which estimated 86 patients with 95% power and a 0.05 significance level.[6] Considering the possibility of patient dropout, the sample size was increased to 110 patients. Of these, 10 patients declined to participate, and 8 patients were excluded due to postoperative intensive care requirements. Consequently, the study was conducted with 92 patients.

## Results

A total of 92 patients were included in the study. Most participants were aged 18–65 years (96.7%), 55 female patients (59.8%), and married or remarried (82.6%). A considerable proportion had high school or higher education (60.9%). More than half resided in districts (51.1%), and the majority lived with their spouse and/or children (83.7%). Most participants had not undergone surgery in the last six months (94.6%), and for the majority, this was their first pituitary surgery (81.3%). The demographic characteristics of the patients are presented in Table 1.

**Table 1.** Demographic characteristics of the patients

| Characteristic | Category | n (%) |
|---|---|---|
| **Age** | 18–65 | 89 (96.7) |
| | >65 | 3 (3.3) |
| **Gender** | Female | 55 (59.8) |
| | Male | 37 (40.2) |
| **Marital Status** | Married/Remarried | 76 (82.6) |
| | Divorced/Single | 16 (16.4) |
| **Education Level** | Eliterate | 6 (6.5) |
| | Primary Education | 25 (27.2) |
| | Secondary Education | 5 (5.4) |
| | High School | 26 (28.3) |
| | Higher Education and above | 30 (32.6) |
| **Surgery Experience in Last 6 Months** | Yes | 5 (5.4) |
| | No | 87 (94.6) |
| **Is this the First Pituitary Surgery?** | Yes | 74 (81.3) |
| | No | 18 (18.7) |

The total SMMT score showed a significant decrease in the early postoperative period (1st and 4th hours) compared to the preoperative period, partially recovered at the 24th hour, and returned to preoperative levels by the 1st month (p<0.001). Similarly, slight decreases were observed in orientation and registration memory scores in the early postoperative period, which returned to baseline levels by the 1st month (p<0.001). In the domains of attention and calculation, as well as recall, a marked decline was observed in the early period, followed by partial improvement in the subsequent hours and at the 1st month (p<0.001). Language scores showed a slight decrease in the early postoperative period and remained relatively stable in later measurements (p<0.001) (Table 2).

**Table 2.** Comparison of SMMT scores across measurement times

| Parameter | Preop. | Postop. 1st hour | Postop. 4th hour | Postop. 24th hour | Postop. 1st month | p-value | Significant comparisons |
|---|---|---|---|---|---|---|---|
| **Total Score** | 26.00 (24.0028.00) | 24.00 (21.00–26.00) | 24.00 (22.00–27.00) | 25.00 (22.00–27.75) | 26.00 (23.00–28.00) | <0.001 | A, B, C, D, E, F, G, H |
| **Orientation** | 10.00 (9.00–10.00) | 9.50 (8.00–10.00) | 9.50 (8.00–10.00) | 9.50 (8.00–10.00) | 10.00 (8.00–10.00) | <0.001 | A |
| **Registration Memory** | 3.00 (3.00–3.00) | 3.00 (2.00–3.00) | 3.00 (2.00–3.00) | 3.00 (2.25–3.00) | 3.00 (3.00–3.00) | <0.001 | A |
| **Attention and Calculation** | 4.00 (2.00–5.00) | 2.00 (1.00–4.00) | 2.50 (2.00–4.00) | 3.00 (2.00–5.00) | 3.00 (2.00–5.00) | <0.001 | A, B, D, E, G |
| **Recall** | 2.00 (2.00–3.00) | 2.00 (1.00–2.00) | 2.00 (1.00–2.00) | 2.00 (2.00–3.00) | 2.00 (2.00–3.00) | <0.001 | A, D, E, G |
| **Language** | 9.00 (8.00–9.00) | 8.00 (7.00–9.00) | 8.00 (7.00–9.00) | 8.00 (7.00–9.00) | 8.00 (8.00–9.00) | <0.001 | A, B |

Abbreviations and Notes: Preop.: Preoperative SMMT scores ,Postop. 1st hour / 4th hour / 24th hour / 1st month: Postoperative SMMT scores at specified times
Significant pairwise comparisons: A: Preop. vs Postop. 1st hour ,B: Preop. vs Postop. 4th hour ,C: Preop. vs Postop. 24th hour , D: Postop. 1st hour vs 24th hour
E: Postop. 1st hour vs 1st month, F: Postop. 4th hour vs 24th hour, G: Postop. 4th hour vs 1st month, H: Postop. 24th hour vs 1st month

Male patients had significantly higher preoperative total SMMT scores, orientation, and attention/calculation scores compared to female patients (p<0.05). At the 1st postoperative hour, males continued to show significantly higher total scores and attention/calculation scores (p<0.05). No significant differences between genders were observed in registration/memory, recall, or language domains (Table 3).

**Table 3.** Preoperative and Postoperative 1st Hour SMMT Scores by Gender

| Parameter | Female (n) | Male (n) |
|---|---|---|
| **Preoperative** | | |
| Total Score | 26 (23–27) | 28 (25–29.5)* |
| Orientation | 9 (8–10) | 10 (9–10)* |
| Registration/Memory | 3 (3–3) | 3 (3–3) |
| Attention/Calculation | 3 (2–5) | 5 (3–5)* |
| Recall | 2 (2–3) | 2 (2–3) |
| Language | 9 (8–9) | 9 (8–9) |
| **Postoperative 1st Hour** | | |
| Total Score | 22 (21–25) | 25 (22–27)* |
| Orientation | 9 (8–10) | 10 (9–10) |
| Registration/Memory | 3 (2–3) | 3 (2–3) |
| Attention/Calculation | 2 (1–3) | 3 (2–4)* |
| Recall | 1 (1–2) | 2 (1–3) |
| Language | 8 (7–9) | 8 (7.5–9) |

*p<0.05 compared to female

No statistically significant differences were observed between having undergone surgery in the last 6 months and SMMT scores (p>0.05) (Table 4) (Figure 1).

**Table 4**. Postoperative 1st Hour SMMT Scores According to Surgery History in the Last 6 Months*

| Parameter | Surgery in last 6 months | Other patients |
|---|---|---|
| Total Score | 27 (19.5–27.5) | 24 (21–26) |
| Orientation | 10 (8.5–10) | 9 (8–10) |
| Registration/Memory | 3 (2–3) | 3 (2–3) |
| Attention/Calculation | 2 (1–4.5) | 2 (1–4) |
| Recall | 1 (1–2.5) | 2 (1–2) |
| Language | 8 (7–9) | 8 (7–9) |

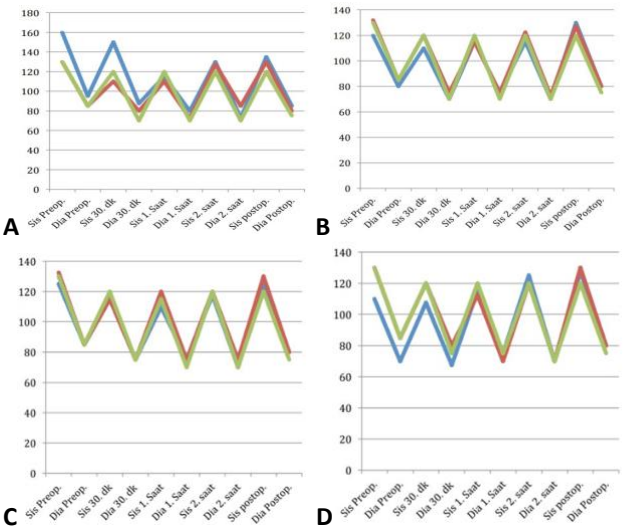
*Mann–Whitney U test was used; p > 0.05.

No statistically significant differences were observed in SMMT scores between patients who had undergone their first pituitary surgery and those who had not (p>0.05) (Table 5).

**Table 5**. Postoperative 1st Hour SMMT Scores According to First Pituitary Surgery*

| Parameter | First pituitary surgery | Other patients |
|---|---|---|
| Total Score | 23 (21–26) | 24 (21–26.5) |
| Orientation | 9 (8–10) | 10 (8.5–10) |
| Registration/Memory | 3 (2–3) | 3 (2–3) |
| Attention/Calculation | 2 (1–4) | 2 (2–3) |
| Recall | 1 (1–2) | 2 (1–2) |
| Language | 8 (7–9) | 8 (7–9) |

*Mann–Whitney U test was used; p > 0.05.



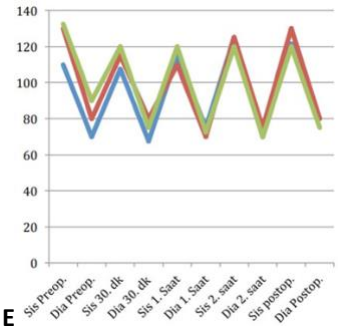




**Figure 1.** Distribution of cognitive impairment according to blood pressure values ((A) Preoperative., (B) Postoperative 1st hour., (C) Postoperative 4th hour., (D) Postoperative 24th hour. (E) Postoperative 1st month.). Blue line: SMMT score (0-17) Red line: SMMT score (18-23) Green line: SMMT score (24-30)

## Disccusion

The most important findings of our study are that patients' SMMT total and registration memory scores significantly decreased at the 1st postoperative hour but returned to preoperative levels over time, indicating that greater attention should be paid to cognitive impairment in the early postoperative period. Orientation was relatively unaffected postoperatively, whereas attention and calculation, recall, and language domains were more prominently impaired. In the gender-based evaluation, male patients had higher preoperative total, orientation, and attention and calculation scores; however, postoperative cognitive dysfunction was more frequently observed in female patients. Additionally, no significant relationship was found between blood pressure values and postoperative cognitive dysfunction.

In our study, patients' SMMT total and registration memory scores were found to decrease significantly in the early postoperative period, particularly within the first hours, but these values approached preoperative levels during follow-up. This finding indicates that the early postoperative period is the most vulnerable phase in terms of cognition. Indeed, current studies report that cognitive functions are generally temporarily affected in the early postoperative period, but stabilize or improve in the following weeks and months. Specifically, follow-up assessments at three months generally show that cognitive performance returns to baseline levels or shows improvement in some patients .[7] This situation is explained not by the direct effects of anesthesia, but rather by the resolution of perioperative stress factors and the improvement of the patient's physiological condition.

The relatively minor impact on the orientation subdomain in the postoperative period indicates that cognitive functions are not affected homogeneously. Current literature also emphasizes that cognitive changes follow a heterogeneous course and that different cognitive domains exhibit varying sensitivity to surgery and anesthesia. Within the framework of perioperative neurocognitive disorders, this heterogeneity is defined as a fundamental characteristic, noting that cognitive changes do not occur uniformly across all domains.[7,8]

Conversely, in our study, the attention and calculation, recall, and language subdomains were more prominently affected postoperatively. Literature also reports that domains such as attention and memory are particularly sensitive to postoperative changes. Recent studies examining cognitive outcomes after pituitary surgery indicate that, although overall cognitive functions generally remain stable or improve, differences may exist in individual subdomains.

These differences may be influenced by factors such as hormonal status, fatigue, and neuroendocrine changes .[9,10]

In the gender-based evaluation, male patients had higher preoperative SMMT total, orientation, and attention-calculation scores compared to female patients. Additionally, the observation that cognitive decline was more pronounced in female patients postoperatively suggests that gender may be an important risk factor. This finding is consistent with current literature. Recent studies show that biological sex may influence susceptibility to postoperative cognitive changes through mechanisms such as neuroinflammation, hormonal regulation, and cognitive reserve .[11] Some studies report that early postoperative cognitive decline is more pronounced in female patients, although this difference may decrease over time. Accordingly, the higher rate of postoperative cognitive dysfunction (POCD) observed in female patients in our study may be explained by both baseline cognitive differences and sex-specific biological responses.

No significant relationship was found between patients' place of residence, history of surgery within the last six months, or whether it was their first operation, and SMMT scores. This finding indicates that postoperative cognitive outcomes cannot be explained by a single demographic or surgical history variable. Current literature supports that the course of cognition is highly heterogeneous and is more closely related to baseline cognitive status, comorbidities, and individual physiological reserve .[7,12] Therefore, previous surgical history alone is not considered a strong determinant.

Finally, no significant relationship was found between blood pressure values and postoperative cognitive dysfunction in our study. Current literature indicates that the impact of intraoperative hypotension on cognitive outcomes is unclear and cannot be considered an independent risk factor on its own. Particularly in patients undergoing pituitary surgery, cognitive outcomes are influenced by the interplay of multiple factors, including hormonal status, tumor characteristics, and perioperative stress .[7,13] In this context, the absence of a relationship between blood pressure and POCD in our study supports the multifactorial nature of cognitive outcomes.

In conclusion, this study demonstrates that cognitive changes after pituitary surgery are temporary, domain-specific, and multifactorial. It emphasizes the need for careful cognitive assessment, particularly in the early postoperative period, highlights gender as a potential risk factor, and shows that hemodynamic variables alone are not determinative. These findings are consistent with the current conceptual framework of perioperative neurocognitive disorders and support the necessity of individualized evaluation in clinical follow-up.

**Conflict of Interest**

The authors declare that they have no conflicts of interest.

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**Author Contributions**

All authors contributed to the conception and design of the study, data collection and analysis, interpretation of the results, drafting and critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

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