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ORIGINAL RESEARCH

Association Between Preoperative Mechanical Bowel Preparation and Postoperative Cognitive Dysfunction in Patients Undergoing Colorectal Surgery: A Pilot Randomized Controlled Trial

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Introduction: Postoperative cognitive dysfunction (POCD) is a common condition that greatly threatens patients' quality of life. While mechanical bowel preparation (MBP) enhances surgical visibility, its effect on postoperative complication rates remains debated. This study aims to evaluate the effect of MBP on POCD in patients undergoing colorectal surgery and to investigate its association with tau protein, brain-derived neurotrophic factor (BDNF) and lipopolysaccharide-binding protein (LBP) levels.

Methods: This is a single-center randomized controlled trial. 80 eligible ASA–PS II–III colorectal surgery patients were randomized into his pilot study, which was designed as a randomized controlled trial. Cognitive function was assessed preoperatively (T1), postoperatively on day 15 (T2), and on day 90 (T3) using the Montreal Cognitive Assessment (MoCA). Blood samples were collected simultaneously from the patients for biomarker analysis. A decline of > 1 standard deviation from baseline on the MoCA was defined as POCD.

Results: The incidence of POCD was significantly lower in patients without MBP compared to those with MBP (7.5% vs. 55%). At T3, BDNF levels were significantly higher in Group I than in Group II ($p < 0.001$). LBP levels were significantly higher in Group II than in Group I at T3 ($p = 0.001$). In patients with POCD, tau protein levels were significantly higher at T2 and T3 ($p = 0.007$; $p = 0.012$), while BDNF levels were significantly lower at T3 ($p < 0.001$).

Conclusion: MBP was associated with a higher incidence of POCD in patients undergoing colorectal surgery; however, these preliminary findings require confirmation in larger trials.

Keywords: biomarker, colorectal surgery, mechanical bowel preparation, MoCA test, postoperative cognitive dysfunction

Introduction

Postoperative cognitive dysfunction (POCD) is a common and potentially debilitating complication following surgery, characterized by impairments in memory, attention, concentration, and other cognitive domains.[1] With the progressive aging of the global population, the number of surgical procedures performed each year continues to increase, accompanied by a growing prevalence of POCD. Although the pathophysiology of POCD has not been fully elucidated, understanding its underlying mechanisms is essential for developing preventive strategies, improving postoperative recovery, and reducing healthcare costs.[2,3]

Neuroinflammation is widely recognized as a central mechanism underlying POCD, with systemic inflammation, blood–brain barrier dysfunction, and microglial activation playing key roles in postoperative cognitive decline.

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Increasing evidence suggests that perioperative alterations in the gut microbiota may amplify these processes through the gut–brain axis. Disruption of intestinal microbial homeostasis can compromise intestinal barrier integrity, allowing bacterial products such as lipopolysaccharide (LPS) to enter the systemic circulation and trigger a pro-inflammatory response. This inflammatory pathway may promote synaptic dysfunction, neuronal injury, and cognitive impairment, providing a biologically plausible link between perioperative gut dysbiosis and POCD.[3,4] Experimental studies further support this concept, demonstrating that anesthesia-induced gut microbiota dysregulation promotes neuroinflammation and cognitive impairment, while recent reviews have highlighted the gut–brain axis as a potential mechanistic pathway underlying perioperative neurocognitive disorders.[5]

The use of mechanical bowel preparation (MBP) in colorectal cancer surgery continues to be a matter of debate. Currently, there is no robust evidence strongly supporting the clinical benefits of MBP when combined with conventional systemic antibiotic prophylaxis in colon surgery. On the contrary, a 2024 meta-analysis strongly recommended against the routine use of MBP, as it did not reduce postoperative complications in patients undergoing colon surgery.[6] Nevertheless, many surgeons prefer MBP due to its technical advantages, such as easier bowel movement, increased detection of small tumors and polyps, and facilitating colonoscopy during surgery. A recent pilot study demonstrated that mechanical bowel preparation significantly altered the gut microbiota, reducing the abundance of seven bacterial genera that have been associated with intestinal homeostasis and anastomotic healing. In combination with inflammatory changes in the intestinal wall, these microbiota alterations may impair anastomotic healing and increase the risk of anastomotic leakage.[7,8] Beyond its effects on the gut microbiota, MBP may also influence postoperative cognitive outcomes through potential fluid shifts and electrolyte disturbances associated with bowel cleansing, which may contribute to perioperative metabolic imbalance and transient cognitive impairment. Furthermore, these factors may contribute to other postoperative complications, including pneumonia, wound infections, intra-abdominal abscesses, and urinary tract infections.[9] In patients undergoing gastric cancer surgery, the incidence of delirium was compared between those who received MBP and those who did not; results showed that MBP disrupted the gut microbiome and increased delirium incidence.[10]

To further investigate the biological mechanisms linking MBP-induced gut dysbiosis to POCD, we selected three complementary biomarkers representing different components of the gut–brain axis: lipopolysaccharide-binding protein (LBP), a surrogate marker of bacterial endotoxin exposure and intestinal barrier dysfunction; brain-derived neurotrophic factor (BDNF), a key regulator of synaptic plasticity and cognitive function; and tau protein, a marker of neuronal injury. Together, these biomarkers may provide mechanistic insight into the relationship between gut-derived inflammation and postoperative cognitive dysfunction.[11–13]

Numerous postoperative complications after colorectal cancer surgery have been linked to the gut microbiome. However, this study is the first to investigate the effect of MBP on POCD.

We hypothesized that mechanical bowel preparation disrupts the gut microbiota, leading to gut-derived inflammation and an increased risk of POCD. We further hypothesized that these effects would be reflected by alterations in circulating LBP, BDNF, and tau protein levels. This study aimed to evaluate the effect of MBP on POCD in patients undergoing colorectal surgery and to explore its association with relevant biomarkers. This pilot study was designed to provide preliminary data for future confirmatory studies.

Methods

Patient Population

This single-center, prospective, randomized pilot clinical trial was conducted at Erciyes University Faculty of Medicine Hospital between July 2023 and July 2024, following approval from the Erciyes University Clinical Research Ethics Committee (decision number 2022/785). This study was supported by the Turkish Health Institutes Presidency (2022 A 08–22532). The study was registered at clinicaltrials.gov (NCT05942404; first registration date: 2023.06.14) and was conducted and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. All procedures were performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants prior to their participation (Figure 1).

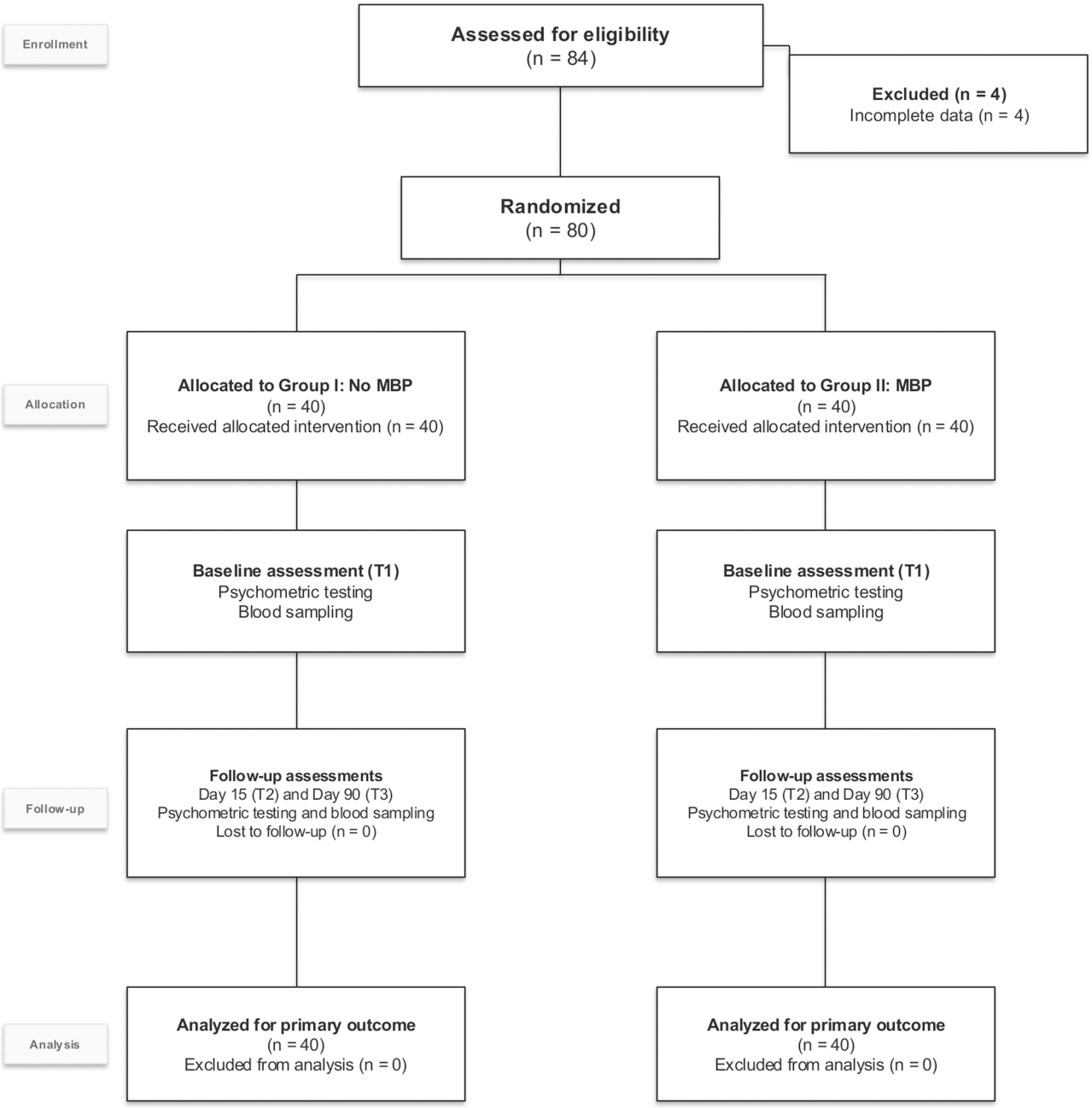


Figure 1 CONSORT diagram.

This study included male patients aged 45–80 years with American Society of Anesthesiologists (ASA) physical status II–III who were scheduled for elective colorectal cancer surgery.

Exclusion criteria included: inflammatory bowel disease; prior colorectal surgery; history of cerebrovascular disease; diagnosed neurodegenerative disorder; moderate-to-severe cognitive impairment (Montreal Cognitive Assessment [MoCA] score $\leq$ 21 or Standardized Mini-Mental State Examination [SMMSE] score $\leq$ 23); inability to complete neurocognitive testing; severe visual or hearing impairment; antibiotic or probiotic use within 4 weeks before surgery; long-term corticosteroid therapy ($\geq$ 7 consecutive days); immunosuppressive treatment; chronic alcohol consumption history; emergency surgery; and refusal to participate.

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Randomization and Blinding

Randomization was performed using a computer-generated sequence, and patient allocation to groups was concealed in sealed envelopes. The anesthesiologists responsible for perioperative management and the psychiatrist who conducted the perioperative cognitive assessments were blinded to treatment allocation throughout the study. The psychiatrist had no access to the randomization sequence and was not involved in perioperative patient management. Because mechanical bowel preparation is an inherently apparent intervention, blinding of participants was not feasible.

Perioperative Management

Patients were randomized into two groups: no mechanical bowel preparation (MBP, Group I, n = 40) and MBP (Group II, n = 40). The night before surgery, Group I patients underwent preoperative fasting for 6–8 hours, while Group II patients received standard MBP in addition to the same fasting protocol. The MBP regimen consisted of 135 mL of sodium phosphate solution administered rectally three times, followed by 125 mL of sennoside A and B solution administered twice at two-hour intervals. Standard care included routine preoperative assessments, vital sign monitoring, and fasting instructions. Standard monitoring (heart rate, non-invasive blood pressure, peripheral oxygen saturation, and temperature) was applied. An epidural catheter was inserted at the sitting position via a paramedian approach to the T9-T10 interlaminar epidural space. A test dose with lidocaine and epinephrine was given through the epidural catheter to exclude subarachnoid and intravascular placement. Correct placement was verified with sensory loss to cold sensation on corresponding dermatomes. Induction was achieved with propofol (2–2.5 mg/kg), fentanyl (1–2 μg/kg), and rocuronium (0.6 mg/kg), followed by endotracheal intubation. Neuromuscular function and entropy (GE Healthcare, Finland) were monitored throughout the procedure. Anesthesia was maintained with desflurane (3–6%, MAC 0.8–1.0) in a 50:50 oxygen–air mixture at 2 L/min, maintaining entropy levels between 40 and 60. Intraoperative analgesia was provided with a remifentanil infusion (0.05–1 μg/kg/min). For postoperative analgesia, patients received 3 mg of morphine diluted in 15 mL of saline via the catheter twice daily in the postoperative period. If NRS ≥ 4, acetaminophen 1 g was given intravenously. If moderate to severe pain (NRS ≥ 4) persisted after 30 minutes, tramadol 100 mg was given intravenously.

Psychometric Testing

Neurocognitive assessments were performed by the same psychiatrist at three time points: preoperatively (before MBP) (T1), postoperative day 15 (T2), and postoperative day 90 (T3). The Montreal Cognitive Assessment (MoCA), Standardized Mini-Mental State Examination (SMMSE), and Hospital Anxiety and Depression Scale (HADS) were administered concurrently. The maximum MoCA score was 30; scores ≥ 21 were considered normal.[14,15] For HADS, cut-off scores were 10 for the anxiety subscale (HADS-A) and 7 for the depression subscale (HADS-D), with higher values indicating risk for anxiety or depression.[16] The SMMSE was scored on a 30. Scores of 24–30 were considered indicative of normal cognitive function, whereas scores of 20–23, 10–19, and 0–9 indicated mild, moderate, and severe cognitive impairment, respectively.[17–19] A decline of > 1 standard deviation (SD) from baseline MoCA scores was defined as POCD.[20]

Serum Isolation and Enzyme-Linked Immunosorbent Assay (ELISA)

At time points T1, T2, and T3, 2 mL of venous blood was collected concurrently with psychometric testing to investigate the relationship between POCD and serum biomarkers. Blood samples were centrifuged at 3000 rpm for 10 minutes, and the separated serum was transferred to eppendorf tubes and stored at −80°C until analysis. Before analysis, serum samples were thawed and processed according to the manufacturers' instructions.

Serum total tau protein, lipopolysaccharide-binding protein (LBP), and brain-derived neurotrophic factor (BDNF) concentrations were determined using commercially available human enzyme-linked immunosorbent assay (ELISA) kits (SunRed Biological Technology Co., Ltd., Shanghai, China). Total tau protein was measured using the Human Total Tau ELISA Kit (Cat. No. 201–12-1334; sensitivity: 0.175 ng/L; range: 0.2–60 ng/L). Serum BDNF levels were measured using the Human BDNF ELISA Kit (Cat. No. 201–12-1303; sensitivity: 0.05 ng/mL; assay range: 0.1–10 ng/mL). Serum

LBP concentrations were measured using the Human Lipopolysaccharide-Binding Protein ELISA Kit (Cat. No. 201–12-0361; sensitivity: 0.135 μg/mL; assay range: 0.2–60 μg/mL).

All ELISA assays were performed in accordance with the manufacturers' instructions. Standard curves were generated using the supplied standard calibrators, and sample concentrations were calculated from the corresponding standard curves. Absorbance was measured at 450 nm using a Promega Glomax Multi System microplate reader.

Outcome Measures

The primary outcome of this pilot study was the incidence of POCD, defined as a decrease of > 1 SD from baseline MoCA scores.

Secondary outcomes included changes in MoCA and SMMSE scores and in serum levels of tau protein, LBP, and BDNF, measured at the same time points.

Feasibility outcomes included recruitment and retention rates, protocol adherence, and completeness of biomarker data collection. As a pilot study, all outcomes were assessed exploratorily to generate preliminary data and inform the design, sample size, and outcome selection for future larger-scale randomized controlled trials.

Statistical Analysis

Given the absence of prior research on the relationship between MBP and POCD, a formal a priori sample size estimate based on existing effect sizes was unfeasible. The sample size of 40 patients per group was established based on practical feasibility during the one-year recruitment period (July 2023–July 2024) and available funding. The sample size aligns with pilot trial recommendations, which recommend 30–40 participants per group to ensure sufficient precision in estimating effect sizes and variability for subsequent confirmatory studies.[21,22] The results of this pilot study can provide initial data for sample size calculation in future appropriately powered experiments.

Data were analyzed using IBM SPSS Statistics Standard Concurrent User V30 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as frequencies (n), percentages (%), means ± SD, medians, and interquartile ranges. Normality of continuous variables was assessed with the Shapiro–Wilk test, and homogeneity of variances with Levene's test. Group comparisons for normally distributed data were performed using independent-samples *t*-tests, while for non-normally distributed data, the Mann–Whitney *U*-test was used. Repeated-measures two-way ANOVA was applied for longitudinal comparisons, with Bonferroni correction for pairwise comparisons. For non-parametric data, intergroup comparisons were performed using the Mann–Whitney *U*-test, and intragroup comparisons were made using the Friedman test, with the Bonferroni correction applied for post hoc analyses. Categorical variables were compared using chi-square tests (Pearson, Yates, or Fisher's exact test as appropriate). Significant chi-square results were further analyzed with Bonferroni-adjusted two-proportion Z tests. Factors influencing POCD were evaluated using a binary logistic regression model with the forward (Wald) method. A p-value < 0.05 was considered statistically significant.

Results

There were no statistically significant differences between the groups in terms of age, body mass index (BMI), frailty scores, duration and type of surgery, comorbidity rates, mortality, or neoadjuvant therapy rates ($p > 0.05$; Table 1).

The incidence of POCD was 7.5% (n = 3) in Group I and 55% (n = 22) in Group II, representing a statistically significant difference ($p < 0.001$) (Figure 2).

Comparisons of serum biomarkers (tau protein, LBP, and BDNF) within and between groups are shown in Table 2. Tau protein levels did not differ significantly between the groups at any time point ($p > 0.05$). BDNF levels were significantly lower in Group I compared to Group II at T1 ($p = 0.004$). Although there was no significant difference at T2 ($p = 0.394$), BDNF levels were notably higher in Group I than in Group II at T3 ($p < 0.001$). LBP levels were significantly higher in Group II than in Group I at both T1 and T3 ($p = 0.001$). Within groups, BDNF levels in Group I increased significantly at T2 and T3 compared to T1 ($p < 0.001$). Conversely, BDNF levels in Group II at T3 were significantly lower than at T1 and T2 ($p < 0.001$). For LBP, the within-group comparison showed significantly higher levels at T3 compared to T1 and T2 in Group II ($p < 0.001$) (Figure 3).

Table 1 Comparison of Descriptive Characteristics and POCD Rates of Groups

	Group 1 n=40	Group 2 n=40	Test value	*p*
Age (*year*)	63.9±9.2	62.4±7.8	0.856	0.395[†]
BMI, (*kg/m2*)	25.76±2.50	26.98±3.59	1.770	0.081[†]
Frail, n (%)			5.477	0.060[¥]
0 (normal)	14 (35.0)	8 (20.0)		
1-2 pre-frail	20 (50.0)	30 (75.0)		
2-5 frail	6 (15.0)	2 (5.0)		
Surgical duration (min)	160 (90)	150 (40)	0.528	0.597[&]
Surgical outcome, n (%)			6.977	**0.025**[¥]
Anastomosis	37 (92.5)	30 (75.0)		
Colostomy	2 (5.0)	10 (25.0)		
Inoperable	1 (2.5)	0 (0.0)		
Surgical type, n (%)				
Laparotomy/Laparoscopic	25/15 (62.5/37.5)	31/9 (77.5/22.5)	1.488	0.223[Φ]
Comorbidites, n (%)				
±	18/22 (45.0/55.0)	20/20 (50.0/50.0)	0.050	0.823[Φ]

Notes: Statistical analysis: Numerical variables are given as mean±standard deviation or median (interquartile range). [†]: Independent sample *t* test, [&]: Mann–Whitney *U*-test, [¥]: Fisher-Freeman-Halton exact test, [Φ]: Yates chi-square test. Bold values indicate statistical significance ($p < 0.05$).

MoCA, SMMSE, anxiety, and depression scores are detailed in Table 3. At T2 and T3, MoCA and SMMSE scores were significantly higher in Group I than in Group II (T2: $p < 0.001$, $p = 0.002$; T3: $p < 0.001$, $p = 0.001$). Anxiety and depression scores showed no significant difference between groups at any time point ($p > 0.05$).

Table 4 summarizes the comparison of serum biomarker levels between patients who developed POCD and those who did not. Tau protein levels were significantly elevated in patients with POCD at T2 and T3 ($p = 0.007$; $p = 0.012$). BDNF levels were significantly lower in POCD patients at T1 and T3 compared to non-POCD patients ($p = 0.007$; $p < 0.001$). LBP levels did not differ significantly between groups at any time point ($p > 0.05$) (Figure 3).

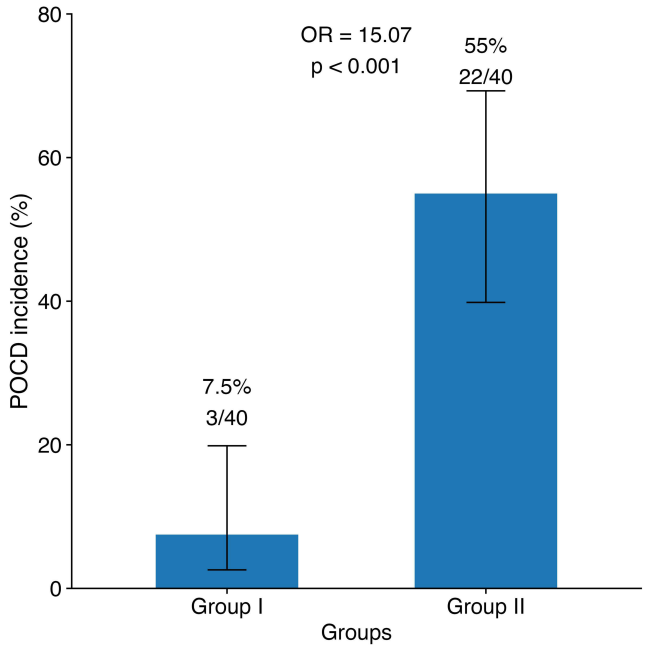


Figure 2 Incidence of POCD.

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Table 2 Comparison of Biomarker Values of Groups According to Measurement Times

	Group 1 n=40	Group 2 n=40	Test value [Ψ]	*p*	*Effect Size*
Tau protein					
T1	10.74 (7.63)	11.58 (3.95)	0.635	0.525[&]	−0.08
T2	10.20 (7.57)	12.00 (6.27)	1.540	0.124[&]	−0.2
T3	10.85 (7.49)	9.90 (9.41)	1.126	0.260[&]	−0.15
Ti[§]: Test and *p* values	4.550; 0.103[#]	1.350; 0.509[#]			
BDNF					
T1	1.26 (0.74)[a]	1.54 (0.95)[a]	2.858	**0.004**[&]	−0.37
T2	1.64 (1.64)[b]	1.57 (0.71)[a]	0.852	0.394[&]	0.11
T3	2.23 (4.27)[b]	1.14 (0.40)[b]	5.283	**<0.001**[&]	0.67
Ti[§]: Test and *p* values	21.950; **<0.001**[#]	29.600; **<0.001**[#]			
LBP					
T1	19.15 (12.09)	8.93 (2.26)[a]	4.811	**0.001**[&]	0.63
T2	13.66 (20.12)	9.23 (2.08)[a]	1.540	0.124[&]	0.2
T3	13.26 (16.28)	21.97 (8.36)[b]	3.705	**0.001**[&]	−0.48
Ti[§]: Test and *p* values	1.850; 0.397[#]	40.950; **<0.001**[#]			

Notes: The data are presented as median (interquartile range). [Ψ]: Between-group comparisons at each time point, §: Within-group comparisons across time points, [&]: Mann–Whitney *U*-test, [#]: Friedman analysis, Effect sizes are presented as Cliff's delta. Positive values indicate higher values in Group 1, whereas negative values indicate higher values in Group 2. Superscripts a and b indicate differences between measurement times within each group. Measurement values with the same superscript are not statistically different. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: BDNF, brain-derived neurotrophic factor; LBP, Lipopolysaccharide-binding protein.

At T3, SMMSE scores were significantly lower in patients with POCD than in those without, though no significant differences were observed at T1 or T2 (T3: $p < 0.001$; T1 and T2: $p > 0.05$). Anxiety and depression scores did not differ significantly between POCD and non-POCD groups at any time point ($p > 0.05$).

Table 5 indicates that patients who underwent MBP had a 15.074-fold higher risk of developing POCD compared to those who did not undergo MBP.

Discussion

In this study, preoperative mechanical bowel preparation (MBP) in patients undergoing colorectal surgery was associated with a higher incidence of postoperative cognitive dysfunction (POCD). Although this observation suggests a possible relationship between perioperative intestinal interventions and postoperative cognitive outcomes, the findings should be interpreted cautiously, as the study design does not allow causal inferences. Nevertheless, the results highlight a potential interaction between perioperative gut-related factors and cognitive function, which may involve mechanisms of the gut–brain axis.

POCD has been reported to occur in approximately 47% of patients undergoing laparoscopic or open colorectal surgery.[23] Multiple perioperative factors may contribute to the development of POCD, including preoperative characteristics such as age and baseline cognitive status, intraoperative variables such as surgical duration, anesthetic exposure, and hemodynamic instability, and postoperative complications such as infection and inflammation.[24] In the present study, perioperative management was standardized to the greatest extent possible to reduce variability related to anesthetic and surgical factors. Additionally, only male patients were included to minimize potential biological variability related to sex differences. Previous research has suggested that neuroinflammatory responses may differ between sexes due to hormonal influences and differences in microglial activation patterns, potentially affecting postoperative neuroimmune responses.[25] Cognitive function was evaluated using the MoCA, which was selected because of its practicality and greater sensitivity than the SMMSE for detecting subtle cognitive impairment. However, we acknowledge that the use of

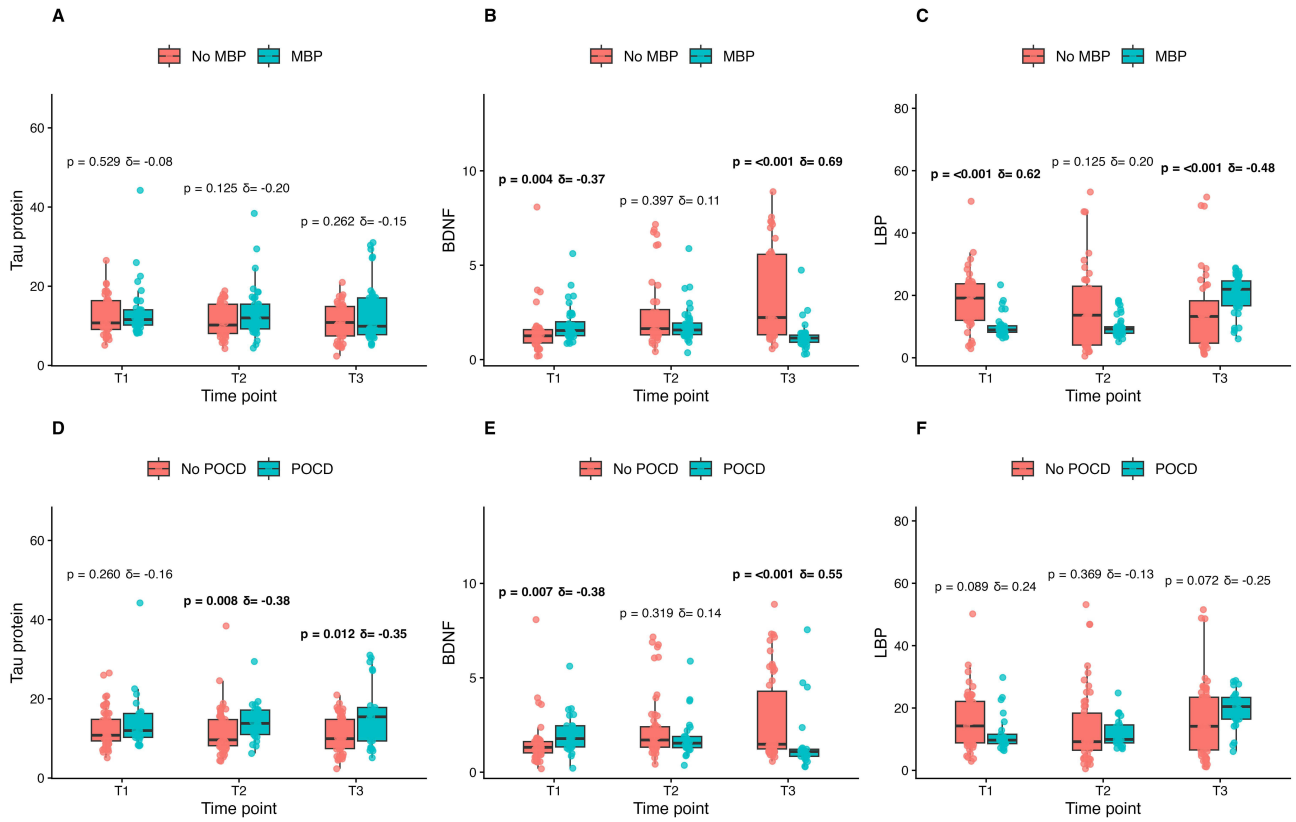


Figure 3 Serum biomarker levels according to groups and POCD status.
Notes: (**A**) Tau protein, (**B**) brain-derived neurotrophic factor (BDNF), and (**C**) lipopolysaccharide-binding protein (LBP) levels by groups (**D**) Tau protein, (**E**) BDNF, and (**F**) LBP levels in patients without and with postoperative cognitive dysfunction (POCD). Measurements were obtained preoperatively (T1), on postoperative day 15 (T2), and on postoperative day 90 (T3). Boxplots display the median and interquartile range; whiskers extend to 1.5 times the interquartile range, and individual points represent patient-level observations. Effect sizes are presented as Cliff's delta (δ). Bold P values indicate statistically significant between-group differences ($P < 0.05$).

a single cognitive screening instrument rather than a comprehensive neuropsychological test battery does not fully align with current consensus recommendations and should be considered when interpreting our findings.[26] Furthermore, defining POCD as a decline of >1 SD from baseline MoCA scores may have increased the risk of misclassification and, consequently, may have influenced the estimated incidence of POCD. Importantly, the higher colostomy rate observed in the MBP group also represents a potential source of confounding. However, additional multivariable and sensitivity analyses that included surgical outcomes demonstrated that colostomy was not independently associated with POCD and did not materially alter the observed association between MBP and POCD. Nevertheless, given the relatively small sample size and limited number of outcome events, residual confounding cannot be completely excluded.

Psychological status before surgery has also been linked to postoperative cognitive outcomes. Preoperative depression and stress have been shown to increase the risk of POCD, while a positive mental state prior to surgery may decrease the chances of postoperative delirium and support better cognitive performance afterward.[3] That's why anxiety and depression scales were included in our study; however, no significant differences were found between groups or between patients with and without POCD.

Several biomarkers have been investigated in relation to POCD.[27] Although these markers are not diagnostic on their own, they may provide insight into biological processes associated with postoperative cognitive changes. POCD is also considered a potentially reversible condition, and its duration may vary among individuals. Therefore, the biomarker measurements obtained at postoperative days 15 and 90 in our study may not fully reflect the entire clinical course.

Tau protein, which is widely recognized as a molecular marker associated with Alzheimer's disease, has been reported to show increased phosphorylation in patients with POCD.[13] Consistent with these reports, postoperative tau protein levels were higher in patients who developed POCD in our study. However, no significant differences in tau

Table 3 Comparison of Psychometric Test Values of Groups According to Measurement Times

	Group 1 n=40	Group 2 n=40	Test value	*p*	*Effect Size*
MoCA					
T1	26.0 (3.0)	25.0 (3.0)	1.512	0.131[&]	0.19
T2	26.0 (3.0)	24.0 (2.8)	3.636	**<0.001**[&]	0.47
T3	25.0 (2.0)	24.0 (4.0)	3.611	**<0.001**[&]	0.46
SMMSE					
T1	27.0 (3.0)	26.0 (3.8)	1.458	0.145[&]	0.19
T2	27.0 (5.0)	24.0 (3.0)	3.168	**0.002**[&]	0.4
T3	26.0 (4.0)	24.0 (3.8)	3.436	**0.001**[&]	0.44
Anxiety					
T1	2.5 (3.0)	3.0 (3.8)	0.166	0.869[&]	−0.02
T2	2.0 (3.0)	2.5 (3.0)	0.044	0.965[&]	−0.01
T3	1.0 (1.8)	2.0 (2.5)	0.568	0.570[&]	−0.07
Depression					
T1	2.0 (3.8)	1.5 (3.0)	0.958	0.338[&]	0.12
T2	2.0 (3.5)	2.0 (2.8)	0.269	0.788[&]	−0.03
T3	1.0 (2.0)	1.0 (3.0)	1.112	0.266[&]	−0.14

Notes: The data are presented as median (interquartile range). [&]: Mann–Whitney *U*-test, Effect sizes are presented as Cliff's delta. Positive values indicate higher values in Group 1, whereas negative values indicate higher values in Group 2. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: MoCA, Montreal Cognitive Assessment; SMMSE, Standardized Mini-Mental State Examination.

Table 4 Comparison of Biomarkers According to Measurement Times in Patients with and Without Postoperative Cognitive Dysfunction (POCD)

	POCD		Tests[Ψ]		
	No n=55	Yes n=25	Test value	*p*	*Effect Size*
Tau protein					
T1	11.81 (5.84)	12.99 (6.07)	1.131	0.258[&]	−0.16
T2	10.64 (6.66)	13.80 (6.45)	2.678	**0.007**[&]	−0.38
T3	9.94 (7.45)	15.46 (9.51)	2.522	**0.012**[&]	−0.35
BDNF					
T1	1.32 (0.61)	1.78 (1.16)	2.714	**0.007**[&]	−0.38
T2	1.71 (1.11)	1.54 (0.77)	1.002	0.316[&]	0.14
T3	1.48 (3.39)	1.09 (0.40)	3.929	**<0.001**[&]	0.55
LBP					
T1	14.25 (13.56)	9.70 (3.64)	1.708	0.088[&]	0.24
T2	9.20 (12.87)	9.93 (6.23)	0.903	0.366[&]	−0.13
T3	16.15 (17.01)	20.4 (7.5)	1.806	0.071[&]	−0.25

Notes: The data are presented as mean±standard deviation or median (interquartile range). Effect sizes are presented as Cliff's delta. Negative values indicate higher values in POCD patients. [Ψ]: Between-group comparisons at each time point, [&]: Mann–Whitney *U*-test, Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: BDNF, brain-derived neurotrophic factor; LBP, Lipopolysaccharide-binding protein.

Table 5 Binary Logistic Regression Analysis of Factors Associated with POCD

	β	Standard Error	Wald Statistics	*p*	Odds Rate	95% Confidence Interval for Odds Ratio	
						Lower	Upper
Constant	−2.512	0.600	17.515	<0.001	0.081		
MBP (+)	2.713	0.679	15.953	<0.001	15.074	3.982	57.069

Notes: Variables included in the model: MBP (Mechanical bowel preparation), age, frailty, surgical outcome.

levels were observed between the MBP and non-MBP groups at any time point. This finding suggests that postoperative tau elevation is more likely to reflect a nonspecific response to perioperative neuronal injury or surgical stress than an effect specifically attributable to mechanical bowel preparation. Therefore, while tau appears to be associated with postoperative cognitive impairment, the relationship between MBP and POCD is likely mediated through other mechanisms.

Brain-derived neurotrophic factor (BDNF) is a key neurotrophic factor involved in neuronal survival, synaptic plasticity, and memory formation. Reduced BDNF levels have been associated with impaired cognitive function and neurodegenerative processes. Decreased BDNF expression has been reported in the early stages of Alzheimer's disease and is correlated with the severity of cognitive impairment.[12] In the present study, postoperative increases in BDNF levels in the non-MBP group may have been associated with a protective response against POCD, whereas decreased BDNF levels observed in patients who developed POCD suggest a potential involvement of BDNF-related pathways in postoperative cognitive impairment. However, the cross-over pattern observed across time points indicates that BDNF dynamics may also be influenced by perioperative factors such as surgical stress and recovery processes. Therefore, these findings should be interpreted cautiously and considered exploratory, requiring confirmation in larger studies.

Lipopolysaccharide-binding protein (LBP) is considered a surrogate marker of circulating lipopolysaccharide (LPS) activity and may indicate increased intestinal permeability and systemic inflammation.[11] In our study, baseline LBP levels were unexpectedly higher in Group I (without MBP). Because baseline blood samples were collected before mechanical bowel preparation, this difference cannot be attributed to the intervention itself and most likely reflects random biological variability despite successful randomization. Nevertheless, LBP levels were higher in the MBP group at the later postoperative time point, suggesting changes in gut permeability related to bowel preparation. However, no significant differences were observed between patients with and without POCD, indicating that although MBP may influence intestinal barrier function, LBP may not be directly associated with postoperative cognitive changes in this population.

Growing evidence suggests that the microbiome–gut–brain axis may play a role in postoperative cognitive outcomes. Alterations in gut microbiota can disrupt both the intestinal mucosal barrier and the blood–brain barrier, potentially promoting neuroinflammation and oxidative stress. These processes may influence the central nervous system through microglia-mediated mechanisms.[28,29] Although desflurane was used as the maintenance anesthetic agent in both groups under a standardized protocol, volatile anesthetics have been associated with neuroinflammatory pathways and may contribute to the overall perioperative cognitive burden.[30] Regulatory mediators such as BDNF and serotonin have also been implicated in microbiota–brain communication.[3] Mechanical bowel preparation has been shown to induce transient dysbiosis, although the clinical consequences of these changes remain unclear.[31] Our findings highlight the need to further explore the possible relationship between perioperative intestinal interventions and postoperative cognitive function.

Limitations

This study has several limitations. It was conducted at a single center with a relatively small sample size, and microbiota analysis was not performed, precluding direct evaluation of MBP-induced alterations in the gut microbiome. In addition, only male patients were included to reduce biological variability, which limits the generalizability of the findings to female patients. Postoperative cognitive function was assessed using the Montreal Cognitive Assessment (MoCA),

a validated and sensitive screening tool; however, the use of a single cognitive instrument rather than a comprehensive neuropsychological test battery may have limited the detection of subtle cognitive changes and does not fully align with current consensus recommendations. The relatively small number of POCD events may have limited the stability of the multivariable regression model despite the use of a predefined variable selection strategy. Furthermore, because multiple exploratory secondary outcomes were analyzed without adjustment for overall multiplicity, some statistically significant findings should be interpreted with caution. Although patients were followed for 90 days, a longer follow-up period may be required to determine the persistence of postoperative cognitive changes. Despite these limitations, the primary aim of this pilot study was to explore the potential association between mechanical bowel preparation and postoperative cognitive dysfunction rather than to establish a comprehensive causal model. Therefore, the findings should be interpreted with caution but may be considered hypothesis-generating and provide preliminary data for the design of future large-scale randomized controlled trials incorporating both sexes, comprehensive neuropsychological assessments, microbiota analyses, and appropriate multivariable statistical models.

Conclusion

Preoperative mechanical bowel preparation in patients undergoing colorectal surgery was associated with a higher incidence of postoperative cognitive dysfunction. While causal relationships cannot be inferred, these findings suggest a potential influence of perioperative intestinal interventions on cognitive outcomes. In addition, patients with POCD demonstrated increased tau protein levels and decreased BDNF levels.

Data Sharing Statement

The data will be available from the corresponding author upon reasonable request.

Ethical Approval

This research has been approved by the research committee of Erciyes University of Medical Sciences (decision number 2022/785), and the study was registered at clinicaltrials.gov (NCT05942404). The study has been conducted in accordance with the principles of the Helsinki Declaration for medical research. Informed consent was obtained from the patients for the collection of their information and the publication of their data, provided they remained anonymous.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests for this work.

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