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Effect of probiotic supplementation during early enteral nutrition on clinical outcomes in severe traumatic brain injury: a randomized, placebo-controlled trial with blinded outcome assessment

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ABSTRACT

Aims: Severe traumatic brain injury (TBI) is associated with substantial morbidity and mortality. Post-traumatic gut dysbiosis may contribute to adverse outcomes, and probiotic supplementation has been proposed as a therapeutic strategy; however, clinical evidence remains inconclusive. This study aimed to evaluate the effect of probiotic supplementation during early enteral nutrition on clinical outcomes in adults with severe TBI.

Methods: This prospective, randomized, placebo-controlled trial with blinded outcome assessment enrolled 54 adults with severe TBI. Participants on an early enteral feeding protocol were randomized to receive either probiotic supplementation (n=27) or a placebo (n=27). The primary outcome was functional status at three months, assessed using the Glasgow Outcome Score Extended (GOSE), or death before assessment. Secondary outcomes included 30-day mortality, complication rates, and intensive care unit (ICU) length of stay.

Results: The mean age was 37±14.9 years, with a male predominance (8:1). Favorable three-month outcomes occurred in 40.7% of the probiotic group compared with 25.9% of controls (p=0.248). The 30-day mortality rate was numerically higher in the probiotic group, though this difference did not achieve statistical significance (22.2% vs. 11.1%; p=0.273). Overall complication rates (51.9% vs. 66.7%; p=0.268), and mean ICU stay (9±3.25 vs. 9±4.14 days; p=0.401) were similar.

Conclusion: Probiotic supplementation during early enteral nutrition demonstrated no statistically significant improvement in three-month functional outcomes or ICU stay in this trial; the primary findings regarding efficacy remain inconclusive, though the observed numerical differences warrant exploration in larger cohorts.

Keywords: Brain injuries; traumatic, enteral nutrition, probiotics, mortality, Glasgow Outcome Scale

INTRODUCTION

Traumatic brain injury (TBI) remains a global health crisis, serving as the leading cause of mortality and lifelong morbidity among individuals aged 18-45 years.[1] Within this spectrum, severe TBI-defined by a Glasgow Coma Scale (GCS) score of 3-8-presents a formidable clinical challenge; despite significant advancements in neurosurgical techniques and critical care, short-term and definitive functional recovery for these patients remain frequently poor.[2,3]

Central to the management of severe TBI is the aggressive optimization of nutritional support, as the injury triggers a profound hypermetabolic and catabolic response that rapidly depletes protein and energy reserves.[4] Early enteral feeding (EEF), typically initiated within 24 to 48 hours of injury, is now recognized as a critical pillar of neuro-intensive care.[5] By delivering nutrients directly to the gastrointestinal tract, EEF helps preserve the structural integrity of the gut mucosa, prevents the "starvation effect" that exacerbates systemic inflammation, and is associated with reduced rates of nosocomial infections and improved survival.[5] Despite these clear benefits, achieving full nutritional targets remains a significant clinical hurdle, as post-traumatic gastrointestinal dysfunction often leads to feeding intolerance, thereby necessitating adjunctive strategies to ensure the success of early nutritional interventions.[6]

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In the pursuit of novel therapeutic targets, recent research has pivoted toward the impact of secondary systemic injuries. Emerging evidence underscores the importance of the microbiota-gut-brain axis, a bidirectional communication pathway through which post-traumatic gut dysbiosis can exacerbate primary neurological injury.[7] Probiotics, defined as live non-pathogenic microorganisms that confer systemic health benefits, have demonstrated the potential to mitigate this dysbiosis across various clinical settings.[8] By reinforcing gut barrier integrity and improving motility, probiotic supplementation is theorized to prevent secondary infectious complications, reduce the systemic translocation of gut-derived neurotoxins, and ultimately improve clinical and functional recovery.[9,10]

However, the current literature regarding the efficacy of probiotics in neurotrauma is characterized by significant heterogeneity. While some investigations report a potential reduction in mortality and systemic inflammation, others indicate no significant effect on survival or long-term disability.[11,12] This lack of consensus, compounded by a marked paucity of prospective data from Sub-Saharan Africa, highlights a critical knowledge gap.

This study aimed to address this deficit by rigorously evaluating the impact of an EEF protocol combined with multispecies probiotic supplementation on major clinical and functional outcomes in adult patients with severe traumatic brain injury. Specifically, we assessed mortality rates and short-term (3-month) recovery metrics associated with probiotic supplementation during an EEF protocol within a Nigerian tertiary care setting, providing essential data on the efficacy of this intervention in a resource-constrained environment.

METHODS

Ethics

This study was approved by the Ethics Research Committee of the University Teaching Hospital in Ilorin (Date: 10.05.2021, Decision No: ERC PAN/2021/10/020). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants prior to their inclusion in the study.

Crucially, all primary and secondary outcome measures were strictly defined a priori before patient enrollment commenced, and no protocol adjustments, criteria modifications, or endpoint revisions were made at any stage during or after the study timeframe.

Informed consent was also obtained from relatives or caregivers for all participants.

Study Design and Population

This study was a prospective, randomized, placebo-controlled trial with blinded outcome assessment conducted at the Division of Neurosurgery, University of Ilorin Teaching Hospital, Kwara State, Nigeria over a 12-month period between January 1, 2023 and December 31, 2023. The study population included all adult patients (aged 18 years and above) presenting to the accident and emergency unit with severe TBI (GCS 3-8) within 24 hours of injury. Exclusion criteria included polytrauma patients (defined as patients sustaining significant injuries to two or more distinct anatomical regions with an Injury Severity Score ≥16) and those with a prior history of probiotic use. Patients with basal skull fractures were also excluded due to the high risk of accidental nasogastric tube misplacement into the intracranial space. Other exclusion criteria included patients with immunocompromised status (e.g., poorly controlled diabetes, HIV), and pregnant patients. A total of 54 eligible patients were recruited.

Sample Size Determination and Randomization

The sample size was calculated using a two-sided test for the comparison of two independent proportions. Based on a previous study from Beck et al.,[13] the expected proportion of unfavorable outcomes in the control group was set at 70%. We hypothesized a clinically meaningful absolute reduction of 40% in the intervention arm, setting the anticipated unfavorable outcome rate for the probiotic group at 30%. Applying a significance level (alpha) of 5% and a statistical power of 80%, the baseline requirement was determined to be 24 patients per group. Accounting for an assumed 10% attrition rate, the final enrollment target was established at 27 patients per group, resulting in a total sample size of 54 participants. The simple random sampling technique was used to allocate patients into either the intervention group or the control group. The random allocation sequence was generated manually by an independent research assistant (a hospital pharmacist) who had no involvement in patient recruitment or clinical care. The research assistant was also responsible for preparing the appropriate agent to be administered in each case i.e. probiotic supplements or sterile water.

To achieve equal block allocation, the pharmacist wrote the group assignments on 54 identical paper slips (27 labeled for the probiotic arm and 27 for the placebo control arm). These slips were mixed in a container and then drawn one by one to populate a master sequence.

Each drawn slip was immediately sealed inside an individual, sequentially numbered, thick opaque envelope. These envelopes were stored securely in the hospital pharmacy. Neurosurgery residents screened and enrolled eligible participants in the accident and emergency unit. After formal enrollment was finalized, the investigator requested the corresponding numbered envelope from the pharmacy, maintaining strict allocation concealment and preventing any selection bias.

Study Protocol and Interventions

The standardized management protocol for severe TBI in our center clinically targets immediate ICU admission for mechanical ventilation, continuous monitoring, stress ulcer prophylaxis, and operative intervention when indicated.

However, due to real-world resource constraints and acute intensive care bed shortages within our setting, universal ICU admission could not be achieved for all participants. While all patients received standardized neurocritical pharmacotherapy, stress ulcer prophylaxis, and surgery when indicated, only 68.5% of the total cohort was managed in the

ICU, while the remaining 31.5% were managed on the general neurosurgery ward, as detailed in our results.

All patients had a size 16 nasogastric (NG) tube passed at admission. The intervention group (group A) received a multispecies tablet form of probiotics, including *Lactobacillus bulgaricus*, *Bifidobacterium longum*, and *Enterococcus faecalis* [six tablets twice daily, delivering a standardized therapeutic dose of 3.0×10^9 colony-forming units (CFUs) per administration]. The tablets were dissolved in 20 ml of sterile water and administered via the NG tube. To mitigate any bias arising from the visual differences between the cloudy probiotic suspension and the clear sterile water placebo, all administrations were handled exclusively by the bedside ward nursing staff. These nurses were entirely un-associated with the research team and played no role in clinical evaluations, treatment decisions, or data collection, thereby preventing any visual unblinding from influencing the study outcomes.

Patients in the control group were administered a placebo (20mls of sterile water twice daily) via the NG tube. An additional 20mls of sterile water was used to flush the NG tube after each dose of the placebo similar to what was done in the intervention arm. The drug and placebo were administered over ten days, commencing on the day of trauma. The probiotic or placebo intervention was initiated on day 1 (within 24 hours of admission), ensuring it was established well before any enteral nutrition commenced. All recruited patients were kept nil per os (NPO) during the first 48 hours post-admission to prioritize primary cardiorespiratory resuscitation, fluid balance, and neuro-intensive stabilization.

Enteral nutrition via the nasogastric tube was formally initiated exactly at the 48-hour mark post-injury, aligning with the upper threshold of EEF guidelines. Due to socio-economic constraints and the high cost of commercial formulas, the feeds consisted of locally prepared, nutrient-dense fortified pap sourced by the patients' relatives. While this formula provided essential macronutrients, the precise daily caloric and protein quantities could not be standardized or individually measured.

The first full 24-hour volume of enteral feeding was completed on the third day of admission, which is why the active feeding schedule is indexed as day 3. This volume-based regimen was successfully tolerated and achieved by approximately 80% of the patients by day 7, progressing according to the following 24-hour tiers:

- Day 3…..125mls of NG tube feeding 6hrly=500mls/day
- Day 4…..250mls of NG tube feeding 6hrly=1000mls/day
- Day 5…..400mls of NG tube feeding 6hrly=1600mls/day
- Day 6…..400mls of NG tube feeding 4hrly=2400mls/day
- Day 7…..500mls of NG tube feeding 4hrly=3000mls/day

Intravenous fluid was reduced at a corresponding rate every day until day 7 when it was discontinued. Patients who did not tolerate this feeding regimen were noted and documented while the feeding schedule was adjusted appropriately to suit such patients. The nasogastric tube was aspirated before each ration of feed was administered. A patient was adjudged not to have tolerated the feed if there was any residual feed aspirated at the time of the next feeding. In that situation, the next feed was skipped while the same schedule for that day was repeated the next day. This was done in conjunction with the nurses who usually fed the patients. While the administering bedside ward nurses were aware of the fluid consistency at the time of delivery, a strict blinded framework was maintained for all other core parties. The patients' relatives, the primary treating neurosurgeons, and the data analysts remained completely blinded to the group assignments throughout the trial.

To secure the integrity of our primary endpoint, the 3-month follow-up evaluation using the Glasgow Outcome Score Extended (GOSE) was conducted by an independent clinical assessor who was completely blinded to the treatment allocation and had no access to the initial ward administration logs.

Unblinding was only done after completion of data collection or earlier in patients with suspected complications of probiotic supplements.

Clinical Outcome Measures

Clinical outcomes were measured using the Glasgow Outcome Score Extended (GOSE), an 8-point scale considered a sensitive measure for TBI recovery. Outcomes were dichotomized into unfavorable (GOSE 1-4) and favorable (GOSE 5-8). This assessment was conducted at three months post-trauma for survivors or at the time of demise for non-survivors. Secondary outcome measureswhich included 30-day mortality rates; lengths of ICU and hospital stay and the frequency of complications such as bed sores, deep venous thrombosis, and surgical site infection in patients while on admission were noted and documented.

Statistical Analysis

Primary and secondary outcome analyses were performed using a strict Intention-to-Treat (ITT) approach encompassing all 54 randomized participants. For the primary 3-month functional outcome evaluation, patients who died prior to assessment were assigned a score of GOSE 1 (death) and categorized within the unfavorable outcome group. Sociodemographic data, clinical and radiological findings (e.g., CT scan results), and outcome scores were recorded in a structured proforma. Data were analyzed using IBM SPSS version 23.0. Data analysis involved comparing proportions and means between the two groups. A p-value of <0.05 was considered statistically significant.

A Consolidated Standards of Reporting Trials (CONSORT) flow chart showing the study progress from enrollment, through allocation, and follow-up, to analysis is shown below **Figure 1**.

RESULTS

Socio-Demographic Characteristics of the Study Population

A total of 54 patients were enrolled in the study, with 27 randomized into the probiotic-supplemented group and 27

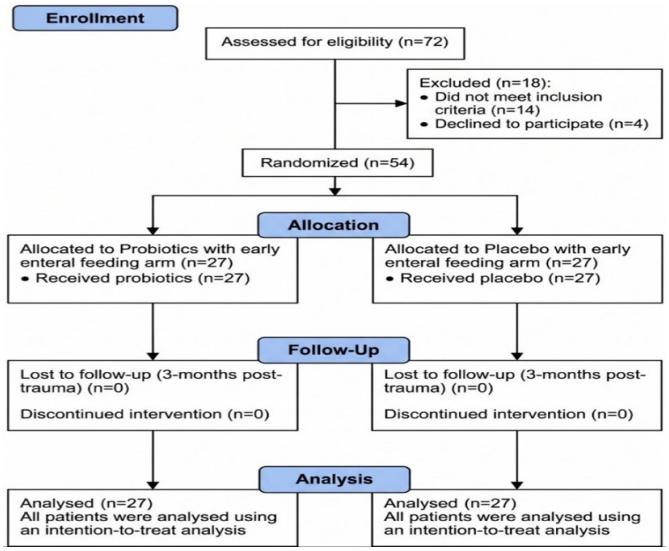

Figure 1. A CONSORT flow chart showing study progress from enrollment, through allocation, and follow-up, to analysis
CONSORT: Consolidated Standards of Reporting Trials

into the placebo group. The mean age of the study population was 37±14.90 years, and 88.9% were males Table 1.

Table 1. Socio-demographic characteristics of the study population n=54

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
Age group (years) n, (%)				1.241	0.743
≤25	7 (25.9)	5 (18.5)	12 (22.2)		
26-35	10 (37.0)	8 (29.6)	18 (33.3)		
36-45	4 (14.8)	6 (22.2)	10 (18.5)		
≥46	6 (22.2)	8 (29.6)	14 (25.9)		
Mean±SD	37±16.2	38±13.8	37±14.9	0.047	0.829
Range	19-75	19-71			
Gender n, (%)				0.001	0.999
Male	24 (88.9)	24 (88.9)	48 (88.9)		
Female	3 (11.1)	3 (11.1)	6 (11.1)		

SD: Standard deviation

Injury mechanism and Cranial CT scan findings

Rider motorcycle road traffic crash was responsible for 51.9% (14 patients) and 55.6% (15 patients) of injuries in the intervention and control groups respectively followed by passenger motorcycle crashes accounting for 18.5% (5 patients) and 14.8% (4 patients) in that order Figure 2. The cranial CT scan findings were also comparable with cerebral edema being the commonest finding in both groups (63.0% and 48.1%) respectively Table 2.

Neurologic Symptoms and Signs

The mean post resuscitation GCS was 7.6±0.6 in the intervention group and 7.3±0.9 in the control group. Seizures occurred in 40.7% (11) and 37.0% (10) of patients in the intervention and control groups respectively. In both groups early post-traumatic seizure was commoner, accounting for 72.7% and 70.0% of cases respectively. No patient had late post traumatic seizure in either group. Vomiting was observed in 33.3% and 25.9% of patients in the probiotics and placebo group respectively. Longitudinal tract deficits were present in 66.7% (18) and 70.4% (19) of patients in the two

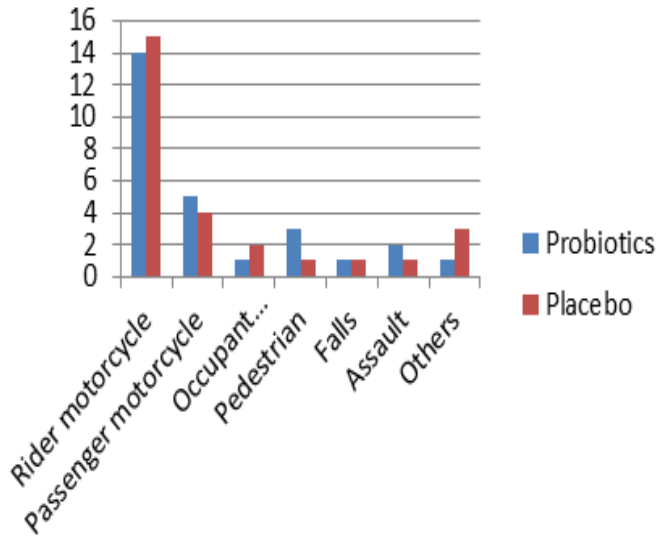

Figure 2. Mechanisms of injury among study participants

Table 2. Cranial CT scan findings in the two groups

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2	p-value
CT scan findings n,(%)					
Fractures	6 (22.2)	11 (40.7)	17 (31.5)	2.146	0.143
EDH	2 (7.4)	5 (18.5)	7 (13.0)	1.477	0.224
ASDH	6 (22.2)	4 (14.8)	10 (18.5)	1.200	0.273
SAH	3 (11.1)	7 (25.9)	10 (18.5)	1.964	0.161
IVH	3 (11.1)	2 (7.4)	5 (9.3)	0.220	0.639
ICH	6 (22.2)	6 (22.2)	12 (22.2)	0.000	1.000
Contusion	12 (44.4)	7 (25.9)	19 (35.2)	2.030	0.154
Edema	17 (63.0)	13 (48.1)	30 (55.6)	1.200	0.273

CT: Computed tomography, EDH: Epidural haematoma, ASDH: Acute subdural haematoma, SAH: Subarachnoid haemorrhage, IVH: Intraventricular haemorrhage, ICH: Intracerebral haemorrhage

groups respectively with hemiparesis being the commonest pattern Table 3, Table 4.

Table 3. Neurologic symptoms among study participants n=54

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
GCS					
At admission	7.1±1.2	7.0±1.0	7.09±1.05	0.128	0.381
Post resuscitation	7.6±0.6	7.3±0.9	7.43±0.77	1.620	0.117
Seizures (n=21)					
Yes	11 (40.7)	10 (37.0)	21 (38.9)	0.078	0.780
No	16 (59.3)	17 (63.0)	33 (61.1)	0.119	0.730[y]
Types of seizure					
Immediate (<24 hours)	3 (27.3)	3 (30.0)	6 (28.6)		
Early (1-7 days)	8 (72.7)	7 (70.0)	15 (71.4)		
Late (>7 days)	0 (0.0)	0 (0.0)	0 (0.0)		
Vomiting				0.355	0.551
Yes	9 (33.3)	7 (25.9)	16 (29.6)		
No	18 (66.7)	20 (74.1)	38 (70.4)		

GCS: Glasgow Coma Scale

Management and Intervention

Among patients in the probiotics group, 77.8% (21) were admitted into the intensive care unit (ICU) while only 59.3%

Table 4. Pupillary sizes, reactivity and long tract deficits

Variables	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
Right pupil size n,(%)				0.250	0.882
<3mm	2 (7.4)	2 (7.4)	4 (7.4)		
3-5mm	22 (81.5)	21 (77.8)	43 (79.6)		
>5mm	3 (11.1)	4 (14.8)	7 (13.0)		
Right pupil reactivity				1.348	0.510
Nil	3 (11.1)	5 (18.5)	8 (14.8)		
Sluggish	10 (37.0)	12 (44.4)	22 (40.7)		
Brisk	14 (51.9)	10 (37.0)	24 (44.4)		
Left pupil size				0.439	0.803
<3mm	3 (11.1)	3 (11.1)	6 (11.1)		
3-5mm	23 (85.2)	21 (77.8)	44 (81.5)		
>5mm	1 (3.7)	3 (11.1)	4 (7.4)		
Left pupil reactivity				0.612	0.736
Nil	2 (7.4)	1 (3.7)	3 (5.6)		
Sluggish	7 (25.9)	9 (33.3)	16 (29.6)		
Brisk	18 (66.7)	17 (63.0)	35 (64.8)		
Long tract deficit				0.085	0.770
Present	18 (66.7)	19 (70.4)	37 (68.5)		
Absent	9 (33.3)	8 (29.6)	17 (31.5)		
Specification of long tract deficit (n=37)	n=18	n=19		0.027	0.986[y]
Right hemiparesis	9 (50.0)	10 (52.6)	19 (51.4)		
Left hemiparesis	9 (50.0)	8 (42.10	17 (45.9)		
Quadriparesis	0 (0.0)	1 (5.3)	1 (2.7)		

Table 5. Management and intervention

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
ICU admission n,(%)				2.146	0.143
Yes	21 (77.8)	16 (59.3)	37 (68.5)		
No	6 (22.2)	11 (40.7)	17 (31.5)		
Duration of ICU admission in days				3.890	0.274
1-5	3 (14.3)	3 (18.8)	6 (16.2)		
6-10	10 (47.6)	8 (50.0)	18 (48.6)		
11-15	8 (38.1)	3 (18.8)	11 (29.7)		
≥ 16	0 (0.0)	2 (12.5)	2 (5.4)		
Mean±SD	9±3.25	9±4.14	9.27±3.61	0.302	0.401
Operative management				2.670	0.102
Yes	10 (37.0)	16 (59.3)	26 (48.1)		
No	17 (63.0)	11 (40.7)	28 (51.9)		
IV mannitol administration				0.092	0.761
Yes	19 (70.4)	20 (74.1)	39 (72.2)		
No	8 (29.6)	7 (25.9)	15 (27.8)		
IV furosemide administration				0.092	0.761
Yes	19 (70.4)	20 (74.1)	39 (72.2)		
No	8 (29.6)	7 (25.9)	15 (27.8)		
Side effect of probiotic administration					
Yes	1 (3.7)	0 (0.0)			
No	26 (96.3)	27 (100.0)			

ICU: Intensive care unit, SD: Standard deviation, IV: Intravenous

Table 6. GOSE assessments at discharge and at 3-months post-trauma

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
GOS-E assessment					
At discharge n, (%)				0.912	0.340
Favorable outcome	8 (29.6)	5 (18.5)	13 (24.1)		
Unfavorable outcome	19 (70.4)	22 (81.5)	41 (75.9)	0.070	0.244
Category of unfavorable outcomes				1.273	0.736[y]
Death	6 (22.2)	3 (11.1)	9 (16.7)		
Vegetative state	2 (7.4)	1 (3.7)	3 (5.6)		
Lower severe disability	9 (33.3)	15 (55.6)	24 (44.4)		
Upper severe disability	2 (7.4)	3 (11.1)	5 (9.3)		
3rd month (post trauma)					
Favorable outcome	11 (40.7)	7 (25.9)	18 (33.3)	0.817	0.248
Unfavorable outcome	16 (59.3)	20 (74.1)	36 (66.7)		
Category of unfavorable outcomes				0.596	0.742[y]
Death (GOSE 1)	6 (22.2)	3 (11.1)			
Vegetative state	2 (7.4)	1 (3.7)	3 (5.6)		
Lower severe disability	7 (25.9)	11 (40.7)	18 (33.3)		
Upper severe disability	1 (3.7)	5 (18.5)	6 (11.1)		
Residual neurological deficit at 3 months post trauma				0.007	0.936
Yes	12 (57.1)	14 (58.3)	26 (57.8)		
No	9 (42.9)	10 (41.7)	19 (42.2)		

GOSE: Glasgow Outcome Score Extended

(16) in the placebo group were admitted in the ICU. While 37% (10) of patients in the probiotics arm had operative intervention, 59.3% (16) of patients in the placebo group had surgical intervention, p=0.102. In both groups, a similar number of patients had administration of mannitol and furosemide- 70.4% (19) and 72.2% (20) in the probiotics and placebo arms respectively Table 5.

Primary Outcome: Glasgow Outcome Score Extended (GOSE)

At hospital discharge, an intention-to-treat analysis showed favorable outcomes (GOSE 5-8) in 29.6% (n=8) of patients in the intervention group and 18.5% (n=5) of patients in the control group (p=0.340). At the three-month follow-up, retaining all randomized patients with deaths coded as GOSE 1, favorable outcomes occurred in 40.7% (n=11) of the probiotic group compared with 25.9% (n=7) of controls (p=0.248) Table 6.

Secondary Outcomes: Lengths of ICU and Hospital Stay, 30-Day Mortality, and Incidence of Complications

There was no significant difference in the mean length of ICU stay between the two groups (9±3.25 days vs. 9± 4.14 days, p=0.401). The overall mean duration of hospital stay was 19.5±6.9 days in the probiotic arm compared to 24.0±11.8 days in the placebo arm, showing no statistically significant difference (p=0.051). The 30-day mortality rate was 22.2% in the probiotic group compared to 11.1% in the placebo group (Table 7); however, this difference was not statistically significant (p=0.273), and the two cohorts exhibited comparable baseline injury characteristics on cranial CT imaging (Table 2). The proportion of patients who developed complications during admission was 51.9% in the probiotics group and 66.7% in the placebo group. When broken down

Table 7. Secondary outcome measures

Variable	Probiotic n=27	Placebo n=27	Total n=54	χ^2/t	p-value
ICU admission n,(%)				2.146	0.143
Yes	21 (77.8)	16 (59.3)	37 (68.5)		
No	6 (22.2)	11 (40.7)	17 (31.5)		
Duration of ICU admission in days				3.890	0.274
1-5	3 (14.3)	3 (18.8)	6 (16.2)		
6-10	10 (47.6)	8 (50.0)	18 (48.6)		
11-15	8 (38.1)	3 (18.8)	11 (29.7)		
≥ 16	0 (0.0)	2 (12.5)	2 (5.4)		
Mean±SD	9±3.25	9±4.14	9.27±3.61	0.302	0.401
Length of hospital stay in days					
Mean±SD	19.5±6.9	24.0±11.8		-1.702	0.051
Still alive at 30 days post trauma					
Yes	21 (77.8)	24 (88.9)			
No	6 (22.2)	3 (11.1)			
30-day mortality	22.2 %	11.1 %		1.200	0.273

ICU: Intensive care unit, SD: Standard deviation

by specific types, the incidences in the probiotic group versus the placebo group were chest infection (37.0% vs. 48.1%), bed sores (3.7% vs. 18.5%), surgical site infection (11.1% vs. 7.4%), deep venous thrombosis (DVT) (0.0% vs. 3.7%), and other complications (3.7% vs. 7.4%).

DISCUSSION

The primary objective of this randomized controlled trial was to evaluate the effectiveness of EEF supplemented with a multispecies probiotics on the major clinical outcomes, including neurological recovery (GOSE) and mortality, in adult patients with severe TBI. The principal finding was the lack of a statistically significant difference in favorable outcomes as measured by the GOSE at three months post-trauma between the intervention and control groups (p=0.248). This outcome indicates that while the probiotic group demonstrated a higher numerical rate of favorable recovery, the primary findings remain inconclusive due to the limited statistical power of our single-center design. Therefore, our results should not be interpreted as an absence of effect, but rather as an unconfirmed trend that requires evaluation in a larger sample pool. Our results are consistent with findings from some previous preclinical and clinical studies by Kobra et al.,[14] Tan et al.,[15] and Falcao de Arruda et al.,[16] all of whom reported no significant neurologic benefits or improvements in functional recovery with probiotic administration.

Our study noted a higher numerical incidence of 30-day mortality within the probiotic group (22.2% vs. 11.1%), although this variation was not statistically significant (p=0.273). This result contrasts sharply with other studies which have reported a reduction in mortality rates with probiotic use. Asaadi et al.,[17] in a 2024 systematic review and meta-analysis demonstrated that probiotic therapy significantly reduced the risk of 28-day mortality in TBI patients (OR: 0.53; 95% CI: 0.31 to 0.9). However, Sharif et al.[18] in another systematic review and meta-analysis, which included 65 randomized controlled trials with over 8.000 patients, concluded that probiotics probably had no effect on mortality in critically ill patients (RR, 0.95; 95% CI, 0.87-1.04). The study also found no significant difference in in-hospital mortality in critically ill ventilated subjects receiving probiotics compared to controls. These findings suggest that the impact on mortality might not be universally positive across all patient populations or probiotic formulations.

The numerically higher mortality in the probiotics group in this index study raises a concern about the safety of this protocol in the management of severe TBI which may have ethical implications. However, the observed discrepancy in mortality rates may be attributable to subtle baseline differences in injury severity between the two randomized groups. The probiotic cohort exhibited a higher proportion of patients with severe cranial pathologies, specifically cerebral edema (63.0%vs.48.1%) and acute subdural hematoma (22.2% vs. 14.8%). These findings suggest that patients in the intervention group may have suffered a greater force of impact at the time of injury, which typically elicits a more intense inflammatory response in the brain, including severe cerebral edema, thus predisposing them to higher mortality.[19,20] Furthermore, acute subdural hematoma is consistently associated with a higher mortality rate due to the severe concomitant brain parenchymal injuries these patients usually sustain.[21,22] These key confounding variables are highly capable of driving differential mortality rates within a limited sample size. Given this small cohort size and the fact that our calculated risk ratio confidence interval spans widely (95% CI: 0.557-7.187), this mortality signal likely reflects baseline injury discrepancies rather than definitive intervention-related harm. Beyond these baseline discrepancies, while the cohort was statistically justified by initial power calculations to address the primary objective, it remains a relatively compact, single-center sample when examining secondary safety endpoints. Consequently, the observed mortality distribution might reflect a statistical artifact or chance variation driven by baseline clinical imbalances rather than a reproducible intervention risk. While a consistent harmful signal is biologically unexpected in most ICU settings, critical illness factors unique to severe TBI-such as profound gut ischemia, mucosal barrier dysfunction, or the confounding effects of vasopressors and broad-spectrum antibiotics-could theoretically facilitate rare microbial translocation or skew clinical outcomes. Consequently, this mortality trend likely stems from a complex interaction between injury pathophysiology and systemic ICU variables rather than a reproducible risk inherent to the probiotic itself. Crucially, a defining factor influencing these survival trends is the systemic constraint on intensive care resources. While standard international guidelines mandate immediate ICU admission and mechanical ventilation for all severe TBI patients, bed shortages in our environment restricted universal access.

The resulting imbalance in ICU care-where more patients in the probiotic arm received intensive monitoring than in the control arm (77.8% vs. 59.3%)-adds an extraordinary layer of clinical confounding. Therefore, these results must be viewed strictly as outcomes within a resource-constrained neurocritical care framework, where differences in monitoring levels significantly dictate both mortality and short-term functional recovery.

Ultimately, while our cohort was statistically grounded by initial power calculations, a much larger patient cohort would be highly preferable to control for subtle baseline imbalances and to confidently rule out chance variations in mortality trends within this population.

Our results also showed no significant difference in the mean length of ICU stay between the two groups (p=0.401). This finding is partially supported by some studies that indicated conflicting results regarding ICU length of stay.[23,24] However, other studies have reported significant reductions in ICU length of stay with probiotic use.[25,26] The inconsistency across studies underscores the heterogeneity in study designs, patient populations, and probiotic products used in current research, making direct comparisons challenging.

Regarding general complications during admission, the proportion of patients who developed complications was lower in the probiotic group (51.9%) compared to the non-probiotic group (66.7%); even though this difference did not reach statistical significance (p=0.268). Some other authors reported a similar pattern of complications.[27,28] Ultimately, optimizing overall clinical outcomes and mitigating such systemic complications relies heavily on structured intensive care unit frameworks and standardized neuroprotection protocols for severe TBI patients.[29,30]

Limitations

A major limitation influencing the interpretation and generalizability of our results relates to adherence to standard of care. Standard neuro-critical care guidelines mandate ICU admission for all severe TBI patients for continuous monitoring and mechanical ventilation. However, due to resource constraints and bed availability within our setting, only 68.5% of the total cohort was admitted to the ICU (77.8% in the probiotic group and 59.3% in the control group).

This variation in the location of care introduces potential confounding factors related to the level of monitoring and specialized care received by the participants. Most importantly, because a significant portion of our cohort had to be managed on general wards rather than in a dedicated ICU due to local resource limitations, our findings cannot be directly generalized to healthcare settings with universal ICU admission and standard mechanical ventilation protocols for all severe TBI cases.

Regarding our study population, the single-center nature of our trial restricts immediate external generalizability. While our sample size was calculated a priori using defined assumptions for the primary dichotomized 3-month GOSE endpoint, the relatively compact scale of this single-center cohort limits its statistical power to detect smaller, localized subgroup variations or to confidently resolve secondary safety endpoints such as mortality trends.

Additionally, due to socio-economic constraints and the resource-limited nature of our setting, patients were fed using relative-sourced fortified pap rather than standardized commercial enteral formulas. The inability to quantify the exact daily caloric and protein intake for each participant represents an additional limitation to our nutritional protocol execution.

CONCLUSION

As a result, this randomized, placebo-controlled trial demonstrated no statistically significant functional recovery benefit from combining enteral feeding with this specific probiotic regimen in patients with severe traumatic brain injury.

Although 30-day mortality was numerically higher in the probiotic cohort, this change was not statistically significant, and the lack of distinct functional benefits indicates that routine probiotic supplementation provides no clear efficacy in this framework. Rather than indicating definitive danger, this numerical trend suggests that a cautious approach should be maintained regarding routine probiotic use in severe TBI until larger, adequately powered multicenter trials can thoroughly evaluate its safety and utility profiles.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Research Committee of the University Teaching Hospital in Ilorin (Date: 10.05.2021, Decision No: ERC PAN/2021/10/020).

Informed Consent

Written informed consent was obtained from relatives and caregivers of all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Conceptualization: OOA; Data Curation: OOA; Formal analysis: OOA; Writing-Original Draft: OOA; Writing-Review and Editing: OTO, NAA, OMA, OE, HAY, SAAİ; Supervision: OTO, SAAİ.

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