Increased mortality but delayed time to death among probiotic-treated patients with severe traumatic brain injury: a paradoxical safety signal from an interventional study

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Abstract

Introduction: Severe traumatic brain injury remains associated with substantial morbidity and mortality despite neurosurgical advances. Gut dysbiosis following traumatic brain injury has been implicated in poor outcomes, and probiotics have shown variable effects in mitigating this issue.

Objective: To determine the effect of probiotic supplementation on mortality and time to death among patients with severe traumatic brain injury.

Methods: This double-blind, prospective, randomized controlled trial included 54 adult patients: 27 received probiotics with early enteral feeding, and 27 received early enteral feeding alone (control group). All patients received standard traumatic brain injury care. Outcomes assessed included clinical status using the Glasgow Outcome Score Extended, lengths of stay, complications, mortality rates, and time to death.

Results: Favorable outcomes at discharge did not differ significantly between the intervention (29.6%) and control groups (18.5%) (p=0.244). A paradoxical finding was however observed: while the median survival time (time to event/death) was significantly longer for the probiotics group (16.0 days, 95% confidence interval: 6.4 to 25.6) compared to the placebo group (5.0 days, 95% confidence interval: 0.2 to 9.8) (log-rank p=0.002), the overall 30-day mortality rate was significantly higher in the probiotic group (22.2%) than in the control group (11.1%) (p=0.033).

Conclusion: Probiotic supplementation resulted in a higher 30-day mortality rate in patients with severe traumatic brain injury, despite delaying the time to mortality among those who died. This contradictory outcome represents a significant safety signal that warrants further investigation into the use of probiotics in this critically ill population.

Keywords: Early enteral feeding, Gut dysbiosis, Mortality rates, Probiotics, Severe traumatic brain injury, Time-to-death

INTRODUCTION

Traumatic brain injury (TBI) is a major global public health concern and the leading cause of mortality and long-term disability, particularly among young adults[1]. The global incidence of TBI is estimated at over 50 million cases annually, with severe TBI (GCS ≤ 8) consistently associated with very high rates of poor outcomes[2]. Despite advances in neurosurgical and critical care, including robust guidelines for intracranial pressure management, ventilation, and nutrition, the mortality and morbidity rates for severe TBI remain substantial, prompting a continuous search for novel therapeutic interventions[3]. The consequences of TBI extend far beyond the immediate physical injury, imposing significant emotional and socioeconomic burdens on patients, their families, and society as a whole[4].

Beyond the primary mechanical insult, TBI triggers a cascade of secondary injuries, including neuroinflammation, oxidative stress, blood-brain barrier (BBB) disruption, and disruption of the gut microbiome (dysbiosis)[5]. The gut-brain axis (GBA) is a critical bidirectional communication network linking the intestinal and central nervous systems[6,7]. Following severe TBI, this axis is severely disrupted, leading to increased intestinal permeability ("leaky gut"), bacterial translocation into the bloodstream, and systemic inflammation that exacerbates cerebral injury and impedes neurological recovery[8,9].This systemic impact contributes to a high metabolic rate, poor nutrient absorption, and increased susceptibility to infections, all of which worsen patient prognosis and challenge conventional management strategies. Current clinical guidelines recommend early enteral nutrition (EEN) within 48 hours of injury to meet the heightened metabolic demands and improve clinical outcomes in patients with severe TBI[10,11]. However, a significant challenge in practice is feeding intolerance, such as ileus and gastric retention, which occurs in a high percentage of patients due to the TBI-induced dysautonomia and gut dysbiosis[12].

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This often necessitates delayed or adjusted feeding regimens, leading to malnutrition and further complications like aspiration pneumonia[12,13].

Probiotics—live microorganisms that confer a health benefit when administered in adequate amounts—have emerged as a potential adjuvant therapy to mitigate gut dysbiosis and improve tolerance to EEN[14]. By enhancing gut barrier function, modulating immune responses, and competing with pathogens, probiotics theoretically can reduce infection rates and shorten ICU stays[15,16]. Preclinical animal models have largely demonstrated beneficial effects, showing that probiotic administration can ameliorate neurological dysfunction, reduce brain edema, and decrease neuroinflammation[17,18].

However, human clinical trial data have yielded conflicting and controversial results. While some meta-analyses and randomized controlled trials (RCTs) have reported that probiotic supplementation significantly reduces the risk of infection, gastrointestinal complications, and the length of ICU stay, others have found no significant effect on overall mortality[19–23]. Importantly, the safety of probiotics in severely immunocompromised or critically ill patients remains a concern due to rare reports of bacteremia or fungemia[24,25]. The heterogeneity across studies in terms of probiotic strains, dosages, timing, and study populations makes it difficult to draw definitive conclusions or provide a universal recommendation for routine clinical use.

Given the existing controversies and the lack of conclusive evidence regarding the safety and efficacy of probiotics in this vulnerable population, further high-quality randomized controlled trials are urgently needed. This study aimed to determine the effect of EEN plus probiotic supplementation on the clinical outcome, including mortality rates and survival time, of adult patients with severe TBI in a prospective double-blind trial. We report a paradoxical finding where, despite an improved median time to death, the overall 30-day mortality rate was significantly higher in the probiotic group, raising a critical safety signal for this intervention in severe TBI patients.

METHODOLOGY

Study Setting and Design

This was a prospective, double-blind, randomized controlled trial conducted over a 12-month period (January 1 to December 31, 2023) at the Division of Neurosurgery, University of Ilorin Teaching Hospital, Kwara State, Nigeria. Ethical approval was secured from the institutional Health Research and Ethics Committee, and informed consent was obtained from the patients' legal caregivers.

Patient Population and Recruitment

The study population comprised all consecutive adult patients (aged 18 years and above) admitted to the Accident and Emergency unit with severe TBI (GCS 3–8) within 24 hours of injury onset. Key exclusion criteria were applied, including basal skull fractures, immunocompromised status, pregnancy, concomitant polytrauma, and a prior history of probiotic use. A total of 54 eligible patients were enrolled in the trial.

Randomization and Blinding

A simple random sampling technique was used to allocate patients into two equal groups (n=27 each) using pre-labeled slips contained within sealed envelopes. The intervention group received probiotic supplementation, while the control group received a placebo. A dedicated research assistant (a Pharmacist) was responsible for managing the randomization process, preparing the appropriate agent for administration, and ensuring that all managing physicians, patients, and their relatives remained blinded to group assignment.

Nutritional Protocol and Study Intervention

All participants followed a standardized severe TBI management protocol, including mechanical ventilation in the ICU and stress ulcer prophylaxis. A size 16 nasogastric (NG) tube was inserted upon admission. All patients commenced early enteral nutrition (EEN) via the NG tube on the second day post-trauma (Day 3 of care), following a structured, escalating feeding schedule.

The intervention group received a multispecies probiotic formulation (Lactobacillus bulgaricus, Bifidobacterium longum, and Enterococcus faecalis) administered as six dissolved tablets twice daily via the NG tube for ten days. The control group received an identical volume of sterile water (placebo) administered in the same manner for the same duration.

Data Collection and Outcome Assessment

Data were collected in a structured proforma, including clinical findings and outcome scores.

The primary outcomes for this analysis were the 30-day mortality rate (proportion of patients who died within 30 days of injury) and the time to event (duration from injury to death). The secondary outcome was the Glasgow Outcome Scale Extended (GOS-E) at discharge.

Statistical Analysis

Data analysis was performed using IBM SPSS version 23.0. Comparisons of proportions (e.g., mortality rates at 30 days) were performed using the Chi-square test. For analyzing the time-to-event data, survival analysis techniques were employed. The Kaplan-Meier estimator was used to generate survival curves and calculate median survival times. The Log-Rank test was used to compare the survival distributions between the probiotic and control groups. A P-value of <0.05 was considered statistically significant.

RESULTS

Baseline socio-demographic, clinical and radiological characteristics

A total of 54 adult patients with severe traumatic brain injury were recruited and randomized equally into the probiotic group (n=27) and the control group (n=27). Admission and post-resuscitation GCS scores were comparable between both groups; p =0.381 and 0.117 respectively. Cranial CT scan findings were also similar with cerebral edema, cerebral contusions and skull fractures being the commonest findings – Table 1.

Table 1: Baseline socio-demographic, clinical and radiological characteristics

Variable	Probiotic (n = 27)	Non-probiotic (n = 27)	Total n = 54	χ^2/t	p value
Age group (years), n (%)				1.241	0.743
≤ 45	21(77.8)	19 (70.4)	40 (74.1)		
≥ 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				0.001	0.999
Male	24 (88.9)	24 (88.9)	48 (88.9)		
Female	3 (11.1)	3 (11.1)	6 (11.1)		
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
CT scan findings					
Edema	17 (63.0)	13 (48.1)	30 (55.6)	1.200	0.273
Contusion	12 (44.4)	7 (25.9)	19 (35.2)	2.030	0.154
Fractures	6 (22.2)	11 (40.7)	17 (31.5)	2.146	0.143
ASDH	6 (22.2)	4 (14.8)	10 (18.5)	1.200	0.273
ICH	6 (22.2)	6 (22.2)	12 (22.2)	0.000	1.000

30-day mortality and Survival analysis (Time-to-event)

The 30-day mortality rate was significantly higher in the probiotic group (22.2%) compared to the control group (11.1%) (p=0.033) – Table 2.

Despite this difference in overall 30-day mortality, the survival analysis (time-to-death) revealed that patients receiving probiotics had a significantly longer median survival time of 16.0 days (95% CI: 6.4–25.6 days) compared to 5.0 days (95% CI: 0.2–9.8 days) for the control group. The Kaplan-Meier survival curves, demonstrated a significant difference in the overall survival distributions between the two groups (Log-rank test $x^2(1) = 9.715$, p=0.002) – Table 3 & Figure 1

Table 2: Thirty-day mortality in the two groups

Variable	Probiotic (n = 27)	Non-probiotic (n = 27)	χ^2/t	p value
Still alive at 30 days post trauma [n, (%)]			1.200	0.273
Yes	21 (77.8)	24 (88.9)		
No	6 (22.2)	3 (11.1)		
30-day mortality	22.2 %	11.1 %	4.522	0.033

Table 3: Summary of Survival Outcomes and Comparative Statistics for the two groups

Group	Total N	N of Events (%)	Mean Survival (SE)	Median Survival (95% CI)	Log Rank x^2 (p-value)
Probiotics	**27**	**6 (22.2)**	18.67 (2.80)	16.00 (6.40-25.60)	9.715(0.002)
Placebo	27	3 (11.1)	4.67 (1.45)	5.00 (0.20-9.80)	
Overall	54	9 (16.7)	14.00 (2.98)	13.00 (4.24-21.77)	

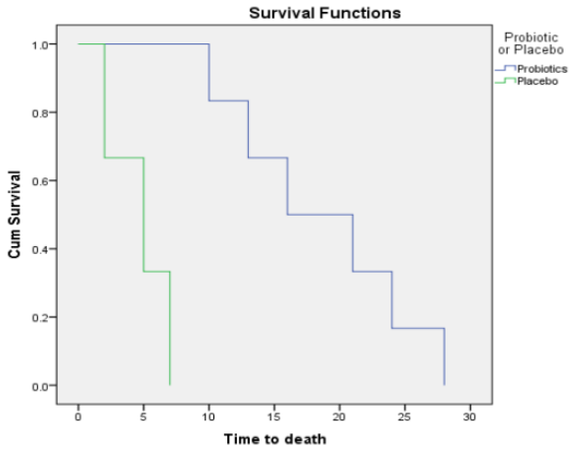

Figure.1: Kaplan-meier survival curves illustrating time to death for the two groups.

Clinical Outcomes at Discharge

At the time of discharge, there was no statistically significant difference in favorable outcomes (GOS-E 5–8) between the two groups with 29.6% (n=8) and 18.5% (n=5) of patients having favorable outcome respectively in the intervention and control groups (p=0.244) – Table 4.

Table 4: Clinical outcome at discharge

Variable	Probiotic (n = 27)	Non-probiotic (n = 27)	Total n = 54	χ^2/t	p value
GOS-E assessment					
At discharge [n, (%)]				0.912	0.340
Favourable outcome	8 (29.6)	5 (18.5)	13 (24.1)		
Unfavourable outcome	19 (70.4)	22 (81.5)	41 (75.9)		
Mean ± SD	4.59 ± 2.11	4.56 ± 1.76	4.57 ± 1.93	0.070	0.244
Types of unfavourable outcomes				1.273	0.736
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)		

DISCUSSION

The findings in this study revealed no statistically significant difference in favorable outcomes at discharge between the probiotic and control groups, which aligns with results of previous studies reporting variable or neutral effects of probiotics on broad endpoints in critically ill populations[26,27]. The novel and striking aspect of our results is the observation of conflicting mortality data within the intervention group.

The Paradox: Higher 30-Day Mortality vs. Delayed Time to Death

The most significant and concerning finding is the divergence between the time-to-event analysis and the fixed-endpoint mortality analysis. We found that the median survival time was significantly longer in the probiotic group (16.0 days vs. 5.0 days in controls, Log-rank test p=0.002), suggesting a potential short-term physiological benefit, possibly related to improved gut function and nutritional absorption or a modulated immune response. This might delay the dying process in some individuals who would otherwise succumb rapidly to the severity of their TBI.

However, this apparent survival duration benefit is starkly contradicted by the significantly higher cumulative 30-day mortality rate in the probiotic group (22.2% vs. 11.1% in controls; p=0.033). This discrepancy highlights a critical statistical consideration in critical care research: standard analyses comparing only survivors' lengths of stay or single fixed endpoints can be misleading if the intervention fundamentally alters the timing of death. Our results suggest that while probiotics might delay the immediate outcome, they ultimately contribute to an increased likelihood of death within a clinically relevant follow-up period. The higher 30-day mortality rate acts as a strong safety signal that warrants clinical caution.

Comparison with Existing Literature and Safety Concerns

Our findings add a cautionary note to the existing conflicting literature regarding probiotic use in critical illness. Some meta-analyses have reported that probiotics may reduce the incidence of ICU-acquired infections, such as ventilator-associated pneumonia (VAP), and shorten ICU length of stay[28,29]. However, these benefits were often found primarily in lower-quality studies, while higher-quality, multi-center randomized controlled trials failed to demonstrate these benefits or any effect on mortality rates[30,31].

Crucially, our results are consistent with known safety concerns,

particularly in highly vulnerable or immunocompromised populations. The landmark PROPATRIA trial, which used a different probiotic strain in severe acute pancreatitis patients, demonstrated significantly increased mortality and adverse events in the intervention arm, leading to early termination of that study[32,33]. Our finding aligns with the growing evidence that the administration of probiotics to critically ill patients may carry risks, including the potential for probiotic-associated fungemia or bacteremia, especially when gut integrity is compromised, a common sequela of severe TBI[34,35]. The specific multi-species formulation used in our study (Lactobacillus bulgaricus, Bifidobacterium longum, Enterococcus faecalis) may interact with the host's compromised immune system in a way that is ultimately deleterious in this specific TBI patient population.

Limitations and Future Directions

The limitations of our study include a relatively small sample size and being conducted at a single center. Future large-scale, adequately powered trials should focus on specific probiotic strains, defined dosages, and standardized patient populations to clarify these safety concerns. Mechanistic studies, including the analysis of changes in the gut microbiome composition and systemic inflammatory markers, are essential to understand how probiotics contribute to this paradoxical mortality outcome and identify subgroups where the therapy might be safe or harmful.

CONCLUSION

In conclusion, the results of this trial indicate that while probiotic supplementation may delay the time to death in critically ill patients with severe TBI, it also significantly increases the overall risk of mortality within 30 days. These findings highlight a critical safety concern and suggest that probiotics may be contraindicated in patients with severe TBI until further evidence confirms their safety in this population. \

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Competing interests: None declared

Ethical approval: This was a prospective study so informed consent was gotten from our institution and all involved participants included in this study.

Conflict of interest: All authors certify that they have no affiliations with or involvement in any organizations or entity with any financial interest, or non-financial interest.

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