Effect of probiotics on the nutritional status of severe stroke patients with nasal feeding that receive enteral nutrition

A protocol for systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Malnutrition is commonly observed after stroke and is closely associated with poor clinical outcomes. So, early nutrition support is particularly crucial for severe stroke patients. However, a significant number of critically ill patients are intolerant to enteral nutrition (EN). Probiotics have been widely used in malnutrition by various diseases and have a low incidence of enteral intolerance. So, we aim to elucidate the efficacy of probiotics in EN in improving the nutritional status and clinical prognosis of severe stroke patients with nasal feeding.

Method: Embase, PubMed, Sinomed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang database, and Vip Journal Integration Platform were searched from inception to March 31, 2021. Randomized controlled trials that applied probiotics in patients with severe stroke were included. The data were extracted and the risk of bias was assessed independently by 2 evaluators.

Results: Twenty-four studies comprising 2003 participants of randomized controlled trials were included. The result of pooled analyses showed that probiotics in EN were associated with better outcomes than EN alone on Glasgow Coma Scale score (mean difference [MD] = 1.03, 95% confidence intervals [CI]: 0.78–1.27; P < .00001), infection events (odds ratio [OR] = 0.25, 95% CI: 0.15–0.43; P < .00001), rate of intestinal flora dysbiosis (OR = 0.24, 95% CI: 0.12–0.48; P < .0001), gastrointestinal complications (OR = 0.25, 95% CI: 0.16–0.37, P < .00001), time to reach target nutrition (MD = −1.80, 95% CI: −2.42 to 1.18, P < .00001), prealbumin content (MD = 25.83, 95% CI: 13.68–37.99, P < .0001).

Conclusion: Our results demonstrated that probiotics supplementation might be an effective intervention for improving the clinical prognosis in severe stroke patients with nasal feeding, but no significant effect on increasing muscle circumference.

Abbreviations: CI = confidence interval, MD = mean difference, OR = odds ratio.

Keywords: enteral nutrition, nutrition status, probiotics, severe stroke

1. Introduction

Malnutrition is commonly observed after stroke and is strongly related to poor clinical outcomes.[1] It is mostly attributed to dysphagia, disorders of consciousness, mobility impairments, and gastrointestinal dysfunction, among which dysphagia is the main risk factor for malnutrition in stroke patients.[2] The prevalence of malnutrition after stroke ranges from 6.1% to 62%.[3,4] The evidence showed that early nutritional status after...
stroke was independently related to long-term prognosis.\[^{2,5}\]\(^\text{1}\)
Malnutrition is often accompanied by low cholesterol levels which weaken immunity by suppressing the innate and acquired immune response, and deteriorate the inflammation response by increasing the expression of proinflammatory factors, which are associated with high incidence of cognitive impairment, disability and mortality after stroke.\[^{6\text{–8}}\]\(^\text{1}\) So, early nutrition support is particularly crucial for severe stroke patients.

Enteral nutrition (EN) is safer than parenteral nutrition and is regarded as a more effective treatment of malnutrition. However, a considerable number of critically ill patients are intolerant to EN,\[^{9}\]\(^\text{1}\) Probiotics have been widely used for malnutrition caused by various diseases without safety issues. Robertson et al\[^{10}\]\(^\text{1}\) confirmed that probiotics intervention could significantly decrease the incidence of necrotising enterocolitis and late-onset sepsis. In neurological disorders, probiotics therapy has shown beneficial clinical effects. A clinical trial found that probiotics in EN therapy were superior to EN alone in reducing gastrointestinal dysfunction and length of intensive care unit stay in patients of severe traumatic brain injury.\[^{11}\]\(^\text{1}\)

However, the effectiveness of probiotics in severe stroke patients with nasal feeding has not been systematically evaluated. So the present study is necessary to fill this gap. The aim of this review is to investigate the effect of the probiotics on nutrition status and clinical efficacy in severe stroke patients with nasal feeding.

2. Methods

This study was undertaken according the PRISMA guidelines, and had registered this review on PROSPERO: CRD42020173643. https://www.crd.york.ac.uk/prospero/.

2.1. Search strategy

We searched Embase (from 1974 to March 31, 2021), PubMed (before March 31, 2021), Sinomed (before March 31, 2021), Web of Science (from 1950 to March 31, 2021), Cochrane Library (before March 31, 2021), China National Knowledge Infrastructure (from 1999 to March 31, 2021), VIP Journal Integration Platform (from 1989 to March 31, 2021), and Wanfang database (before March 31, 2021) for randomized controlled trials that assessed the effect of probiotics in EN on severe stroke patients published. The search was conducted using the following terms: (stroke OR apoplexy OR cerebral hemorrhage OR cerebrovascular accident OR cerebral infarction OR brain infarction OR cerebral haemorrhage OR cerebral apoplexy OR cerebrovascular disease OR brain vascular accident) AND (probiotics OR prebiotics OR symbiotic OR lactobacillus OR synbiotics OR lactobacterium OR bifidobacterium OR lactobacilli OR lactic acid bacteria).

2.2. Study selection

2.2.1. Inclusion criteria.

1. The study design was randomized controlled trials.
2. All subjects were under a clinical diagnosis of severe stroke or Glasgow Coma Scale score <9.
3. Treatment course ≥14 days.

2.2.2. Exclusion standards.

1. Patients with heart, liver, kidney, and other severe organ failure, or malignancy, metabolic diseases.
2. Patients who were allergic to EN or probiotics, and those with mental illness.
3. The study lacking crucial outcome indexes was excluded.

2.3. Data extraction and outcome measures

The data were extracted independently by 2 evaluators using prespecified extraction forms. Any discrepancies were resolved through negotiation by the third evaluator. The following data were extracted from studies: first author, publication year; number of patients (male/female), age, intervention, course of treatment; Glasgow Coma Scale score, infection rate, rate of intestinal flora dysbiosis, gastrointestinal complication, time to reach target nutrition, mid arm muscle circumference, and prealbumin content.

2.4. Risk of bias assessment

The quality of included studies was assessed using the Cochrane Collaboration “Risk of bias” assessment tool,\[^{12}\]\(^\text{1}\) which included aspects as follows: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. Any disagreement was resolved by consulting and discussing among all authors. The scores of modified Jadad Scale vary from 0 to 7 points. An article with Jadad score of 1 to 3 was low-quality and a score of 4 to 7 was high-quality.

2.5. Statistical analysis

Review Manager Software (Version 5.3; Oxford, England) was used for statistical analysis. Categorical data were assessed employing odds ratio (OR) with 95% confidence interval (CI) and continuous data were analyzed using mean difference (MD) with 95% CI. Heterogeneity among studies was assessed by the I-squared (I\(^2\)) test. I\(^2\) ≤ 50% was considered low heterogeneity, and the fixed-effects model was adopted; otherwise, it was deemed to be significant heterogeneity, and the random-effects model was adopted. To avoid biases caused by methodological differences among studies, we used the sensitivity analyses to find the source of heterogeneity and inconsistency. Full-text was evaluated to find the research of the origins of heterogeneity, and investigated its influence on meta-analysis. Publication bias was evaluated by funnel plots when the number of literatures was more than 10. When P < .05, the difference was considered statistically significant.

2.6. Ethical approval

Ethical approval and informed consent of patients were not needed because we only collected data from previous studies that had been published and did not recruit patients.

3. Results

3.1. Study selection

The study selection process was shown in Figure 1. A total of 1225 potentially eligible articles were found through databases. Among them, 1162 publications were excluded for duplication or inconsistent with inclusion criteria by reading the title and abstract. Sixty-three full-texts of articles were reviewed, and eventually 24 articles were included in the final selection.
3.2. Study characteristics

The main characteristics of the included studies were summarized in Table 1. The 24 studies were published between 2013 and 2021. A total of 2003 participants were included in this review, of which 57% were males. A total of 1007 patients were allocated to probiotics supplement with EN. The sample size of each study ranged from 56 to 124, and the participants mostly were 60 to 80 years’ old. The treatment course ranged from 14 to 60 days.

3.3. Quality assessment

Among these 24 studies, 23 studies[13–22,24–35] described detailed random grouping methods. The rest of the researches[23] did not mention specific grouping methods. In incomplete outcome data, selective reporting, and other bias domain, all studies were considered to have a low risk of bias. Also, the included studies in our meta-analysis had unclear risk in terms of the allocation concealment and blinding for outcome assessment. The quality of these articles was presented in Supplementary Table 2, http://links.lww.com/MD/G40.

4. Meta-analysis results

4.1. Glasgow Coma Scale score

Eight trials[16,21,24,27,30–32,35] reported the effect of probiotics on Glasgow Coma Scale score, and the results revealed that probiotics in EN were associated with a significant improvement on Glasgow Coma Scale score (MD = 1.03, 95% CI: 0.78–1.27; \(P\ < .00001\)) without significant heterogeneity (\(I^2 = 46\%\)) (Fig. 2).

4.2. Infection rate

Six trials[13,17,19,22,24,25] showed the effect of probiotics on infection rate; the result suggested that probiotics in EN were associated with lower infection events (OR = 0.25, 95% CI: 0.15–0.43; \(P\ < .00001\)). There was no significant heterogeneity (\(I^2 = 40\%\)) (Fig. 3).

4.3. Rate of intestinal flora dysbiosis

Four trials[14,19,22,35] reported the effect of probiotics on intestinal flora dysbiosis. The pooled result showed a lower incidence of intestinal flora dysbiosis in probiotics group (OR = 0.24, 95% CI: 0.12–0.48; \(P\ < .00001\)) without significant heterogeneity (\(I^2 = 0\%\)) (Fig. 4).

4.4. Gastrointestinal complication

Twelve trials[14,15,18,20,22,23–26,28,31,33] reported the effect of probiotics on gastrointestinal complications, and the pooled analysis revealed that the probiotics in EN decreased the gastrointestinal complications (OR = 0.25, 95% CI: 0.16–0.37; \(P\ < .00001\)) without significant heterogeneity (\(I^2 = 0\%\)) (Fig. 5).
4.5. Time to reach target nutrition

Four trials\cite{19,21,27,36} reported the effect of probiotics on time to reach target nutrition. The pooled result showed that compared to EN alone, probiotics in EN were associated with shorter time to reach target nutrition (MD = −1.80, 95% CI: −2.42 to 1.18 \( P < .0001 \)). There was significant heterogeneity (\( I^2 = 95\% \)) (Fig. 6), but the main outcomes were not affected by excluding any particular study, so the random-effect model was selected.

4.6. Mid arm muscle circumference

Three trials\cite{23,26,31} reported the effect of probiotics on mid arm muscle circumference, and result revealed that probiotics in EN exerted no positive effect on mid arm muscle circumference (MD = 1.76, 95% CI: 0.37–3.89; \( P = .1 \)). There was significant heterogeneity (\( I^2 = 91\% \)) (Fig. 7).

4.7. Prealbumin content

Eight trials\cite{13,16,18,21,27,29,33,34} reported the effect of probiotics on prealbumin content, and the pooled result showed that probiotics were associated with improvement on prealbumin content (MD = 25.83, 95% CI: 13.68–37.99, \( P < .0001 \)). There was significant heterogeneity (\( I^2 = 93\% \)) (Fig. 8), but the main outcomes were not affected by excluding any particular study, so the random-effect model was selected.
Figure 3. Forest plots of effect of probiotics on the infection rate.

Figure 4. Forest plots of effect of probiotics on the rate of intestinal flora dysbiosis.

Figure 5. Forest plots of effect of probiotics on the gastrointestinal complications.

Figure 6. Forest plots of effect of probiotics on the time to reach target nutrition.
4.8. Publication bias

The funnel plot was used to evaluate the publication bias of the 12 randomized controlled trials. Figure 9 showed the publication bias of the whole study was small.

5. Discussion

Our analysis suggested that probiotics had a positive impact on balancing the intestinal flora. The application of probiotics ameliorated gastrointestinal function, nutritional status, and immunity, and what’s more improved Glasgow Coma Scale score, which indicated that probiotics were beneficial in improving the state of consciousness.

The results showed that the time to reach target nutrition was decreased, and prealbumin content was improved in the group of probiotics in EN. This meant that compared to EN alone, probiotics in EN could improve nutrition status. The studies included in this meta-analysis suggested that probiotics in EN reduced the incidence of gut microbiome dysbiosis, protected intestinal mucosal integrity, and alleviated gastrointestinal complications.\(^{14,15,18–22,26,28,31,33,35}\) The mechanism of improving the nutritional status of probiotics was that probiotics could stabilize intestinal homeostasis, accelerate gastrointestinal peristalsis, and inhibit disuse atrophy of intestinal mucosal.\(^{37,38}\) With the restoration of gastrointestinal function, probiotics ultimately facilitated the absorption of nutrients.\(^{39}\) However, the effect on muscle circumference needs to be further validated.

Present researches confirmed that probiotics had positive effect on reducing the incidence of infection and state of consciousness in patients with severe stroke. Infection after stroke, accompanied by inflammatory responses, facilitated the aggregation of proinflammatory cytokines into the region of brain injury and aggravated neurotoxicity.\(^{40–43}\) Research had found that probiotics therapy may be an efficient strategy to induce persistent immune regulation of the central nervous system and reduce neuroinflammation.\(^{44}\) The researches performed by Jin et al\(^{45}\) and Wan et al\(^{46}\) found that probiotics could improve the immunity of critically ill patients, which were consistent with the results of our study. It was important that the reduction of infection rate strongly correlates with improvement of nutritional status.\(^{47–49}\) Besides, our result indicated the improvement in Glasgow Coma Scale score. However, it was not enough to prove the recovery of neurological function. Therefore, further studies are needed to confirm whether probiotics could improve neurological function in patients with severe stroke.

Based on our finding, we found that probiotics supplementation was carried out in the early stage or within 72 hours after stroke. Probiotic formula was also analyzed in this meta-analysis, and it showed that eight studies used Bifidobacterium triple viable, ten studies used Bifidobacterium tetravaccine, and 1 study
added xylooligosaccharides (XOS) to probiotics. Researches showed that XOS could increase Bifidobacteria and fortify the integrity of intestinal epithelium barrier and gastrointestinal absorption function.\cite{30,51} Based on comprehensive analysis, it is recommended to set the course of treatment to ≥14 days. Marzorati M et al\cite{52} found 14-day probiotic intervention had a positive impact on the gut microbiome dysbiosis, as evidenced by a rapid decline in Enterobacteriaceae bacteria and increase of SCFA-producing gut flora. Wu et al\cite{53} also discovered a positive effect of 14-day probiotic intervention on antibiotic-induced intestinal flora dysbiosis. Therefore, we expect our findings to inform the treatment of stroke recovery.

There are several limitations in this meta-analysis. First, all the studies were performed in China. The reason is that probiotics and intestinal flora are a hot topic of research in China. In summary, it was found that the number of articles published on probiotics and intestinal flora from 2015 to 2021 is twice the number published from 2010 to 2015. Secondly, there was significant heterogeneity in the analysis of the 4 indexes, and the heterogeneity might be explained by the difference of the trial design, type of probiotic strains, characteristics of patients, and course of treatment, and the heterogeneity may be a barrier to be accepted widely of our findings. Thirdly, the Glasgow Coma Scale score outcome needs to be interpreted carefully for the scores of the 2 studies not improve\cite{21,32,35} although the difference was statistically significant after combined analysis. In the future, high-quality randomized controlled trials will be required to determine the efficacy of various probiotic formulas with different treatment duration. Also, high-quality trials based on large human cohorts should be designed to clarify the underlying mechanisms of various probiotic formulas in ameliorating nutrition status of severe stroke.

6. Conclusion

In conclusion, our results show that probiotics in EN are useful for improving nutritional status, contributing to the clinical prognosis of severe stroke patients with nasal feeding, and providing clinical evidence for probiotics in the treatment of severe stroke patients. Considering the limitations of our meta-analysis, further research is needed to ensure a high level of evidence demonstrating the beneficial effects of probiotics in enteral nutrition.

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Author contributions

Xiaomin Liu drafted the manuscript. Jiahao Chu and Junzi Long searched related literatures, extracted data and assessed the quality of literature. Jie Zheng, Xue Cheng, and Xinmin Li revised and reviewed the article manuscript. Yasu Zhang had primary responsibility for final content. All authors approved the final manuscript.

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