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EFFECTS OF NUTRITION THERAPY IN OLDER STROKE PATIENTS UNDERGOING REHABILITATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: *Objective:* To systematically review evidence on the effects of nutrition therapy in older stroke patients undergoing rehabilitation and identify its effectiveness using meta-analysis. *Methods:* PubMed (MEDLINE), EMBASE (via Dialog), Cochrane Central Register of Controlled Trial, World Health Organization International Clinical Trials Registry Platform and Ichu-shi Web were searched for relevant articles. Randomized controlled trials investigating the effects of nutrition therapy compared to control interventions in older stroke patients undergoing rehabilitation were considered eligible. The primary outcome was activities of daily living (ADL), and secondary outcomes were all-cause mortality, infections, pneumonia incidence, disability level, walking ability, fall, stroke recurrence, and quality of life. The risk of bias of each trial was assessed using the Cochrane Collaboration Tool, and the quality of the body of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach. *Results:* Eight randomized controlled trials with a total of 5484 participants were included in the meta-analysis. The meta-analysis for ADL showed no significant effects (mean difference, 4.16; 95% confidence interval [CI], -0.88 to 9.20; I^2=53%, low-quality evidence). The meta-analyses for secondary outcomes revealed a significant effect of reduced infections (risk ratio, 0.65; 95% CI, 0.51 to 0.84; I^2=0%; low-quality evidence), with no significant effects on the other outcomes. *Conclusion:* Nutrition therapy had no statistically significant effect on ADL. However, it reduced the incidence of infections. More high-quality trials are warranted to clarify the effects of nutrition therapy in older stroke patients undergoing rehabilitation.

Key words: Nutrition therapy, malnutrition, stroke, rehabilitation, activities of daily living.

Introduction

Stroke can cause serious impairment of physical function, adversely affecting patients' activities of daily living (ADL); it is the third leading cause of disability worldwide (1). A major challenge in stroke patients is malnutrition (2). Many stroke patients develop malnutrition during admission (3), and their nutritional status can worsen during hospitalization (4-6). A systematic review revealed that malnutrition was present in up to 49% of patients after stroke and the incidence increased during rehabilitation (7). Malnutrition was also related to poor outcomes in physical function, mortality, complications, and length of hospital stay in older stroke patients (6, 8, 9). In addition, older stroke patients with greater improvement in nutritional status had higher improvement in ADL (10).

In recent years, stroke-related sarcopenia has been reported (11). Sarcopenia is a geriatric syndrome that presents with generalized low skeletal muscle mass and strength, and is often attributable to malnutrition (12). Sarcopenia can be an independent cause of physical disability (13). Thus, nutritional status might be important and nutritional interventions might be beneficial for rehabilitation outcomes in older stroke patients. As a result, stroke patients could live more independently in the community and medical care costs could be reduced worldwide.

Several review articles have described the effects of nutrition therapy for stroke patients. However, some were monograph (14-16), and only a few systematic reviews have exclusively reported its effect in stroke patients (17, 18). Among these review articles, one published in 2012 assessed the effect of nutritional interventions on ADL using a meta-analysis in stroke patients (18). In this review, ADL was assessed using the dichotomous variable of whether or not death or dependency occurred in a trial. Thus, detailed effects on ADL, such as an ADL score as a continuous variable, and the effects on other rehabilitation outcomes remain unclear. Also in the guidelines for adult stroke rehabilitation and recovery (19), descriptions of the effects of nutrition therapy on rehabilitation outcomes are few and insufficient. Furthermore, adverse events related to nutrition therapy have not been assessed. Thus, it is still unclear whether nutrition therapy is beneficial for stroke patients undergoing rehabilitation. If there are any benefits of nutrition therapy, it might be a worthwhile intervention in addition to therapeutic exercises for these patients. The present review aimed to assess the effects of nutrition therapy in older stroke patients undergoing rehabilitation.

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Methods

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.

Criteria for considering studies for this review

Randomized controlled trials, irrespective of publication type, publication status, date, and language were included. We defined stroke as cerebral infarction, nontraumatic intracerebral hemorrhage, and nontraumatic subarachnoid hemorrhage. Crossover trials were excluded and trials in which participants were undergoing rehabilitation and their mean age was over 65 years were included.

Search methods for identification of studies

PubMed (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (via Dialog), World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp), and Ichu-shi Web, which is a Japanese journal database, were searched for publications from the inception of each database until January 2017. We also searched the reference lists of included trials to identify additional relevant trials. In addition, reports on adverse events due to nutrition therapy were searched. The search strategies are described in the supplementary methods.

Interventions

Nutrition therapy was defined as an intervention for each experimental group. Nutrition therapies included nutritional lectures, counseling, fortified foods, oral nutritional supplements, or parenteral/enteral nutrition. We did not include interventions of micronutrients alone (i.e. vitamin or mineral supplements alone) because our review focused on nutritional intervention involving energy and/or protein. We defined "no intervention", "sham nutritional supplement," and "standard meal provision" as control interventions.

Outcome measures

The primary outcome was ADL measured on validated scales such as the Barthel Index (BI) or Functional Independence Measure (FIM) at follow-up. FIM consists of a motor score and cognitive score, while BI consists of just a motor score. Thus, we decided to use the motor score in FIM for the meta-analysis. Secondary outcomes were all-cause mortality, infections (as defined by the trialists), incidence of pneumonia, disability level using the modified Rankin Scale (mRS), walking ability, fall, stroke recurrence, and quality of life (QOL) measured on any validated scale.

Data collection and assessment of risk of bias

Two independent review authors evaluated each trial. If two authors had a different opinion, they discussed the reasoning behind their decision. When they could not resolve it by themselves, a third review author made the final decision for eligibility. Two review authors independently extracted study characteristics and outcome data from the included trials using data extraction forms that were designed for the review. If there were unclear data, we attempted to contact the trial authors by email. Two review authors assessed the methodological quality of each trial using the Cochrane tool for assessing risk of bias (20). We used the following components: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Any differences in their opinions were resolved through discussion, and a judgment was made based on consensus. We designated the risk of bias for each component as "low," "high," or "unclear."

Statistical analysis

Risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) with 95% CIs for continuous data were calculated. To calculate MDs, the mean and standard deviation (SD) for continuous data in each trial were used. The threshold for significance was set at $P < 0.05$. We identified heterogeneity through visual inspection of the forest plots, the $\chi 2$ test with significance set at $P < 0.10$, and measurements of heterogeneity by I-square statistics (21, 22). For subgroup analyses, we used the type of nutrition therapy. Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration and StatsDirect) was used to pool results with the random effects model and to assess the results for heterogeneity. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of the body of evidence relating to primary and secondary outcomes. This review was prospectively registered with the PROSPERO database of systematic reviews (CRD 42017056512, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017056512).

Results

Results of the search

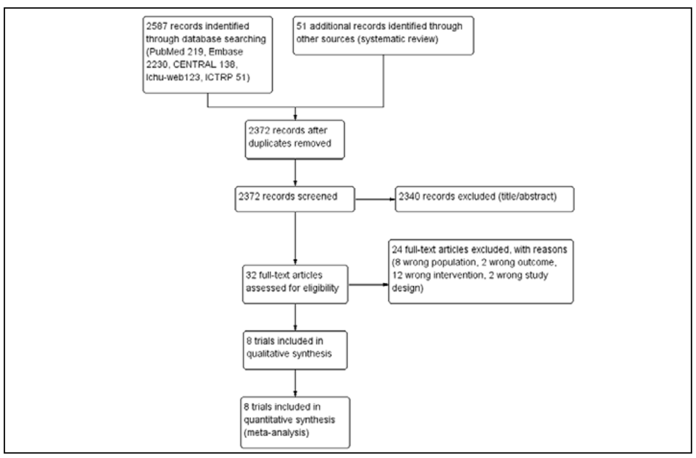
The electronic searches identified 2587 records. An additional 51 records were identified from searches of systematic reviews. We screened a total of 2372 records after removal of duplicates. After screening, 32 potentially relevant studies were identified and assessed for eligibility. Of these, 8 trials were included for qualitative analysis and meta-analysis. The search results are shown in Figure 1.

Included studies and patients

This systematic review identified 8 randomized controlled trials, with a total of 5484 participants. Of the participants, 52.5% (n=2879) were male. One trial (23) accounted for 73.3% of all included participants. From the trials in which data on stroke type was included, 466 of 591 (78.8%) participants were diagnosed with cerebral infarction. This excluded 2 trials (23, 24) lacking data on stroke type. Among all trials, 4 trials (4, 23-25) excluded patients with subarachnoid hemorrhage. As for the stroke phase, 5 trials included acute patients. Among these 5 trials, 2 (4, 24) had patients within 1 week of stroke onset, 1 trial (25) had patients within 72 h of stroke onset, 1 trial (26) had no data on time from stroke onset but descriptions of acute patients. One trial (23) enrolled patients within the first 30 days of admission or within 30 days of a stroke occurring in hospital. However, this trial included patients who were admitted to hospital within 1 day of symptom onset and, according to the results, were randomized a median of 5 days after stroke onset. Thus, it seemed that this study should be considered an acute trial. Other trials included patients within 4 weeks (27), 3 months (28), and a range of days (29) from stroke onset. Three trials (4, 26, 27) included patients with "possible malnutrition". Supplementary Table S1 shows the characteristics of participants in each trial.

Figure 1

Flow diagram showing the process for article selection



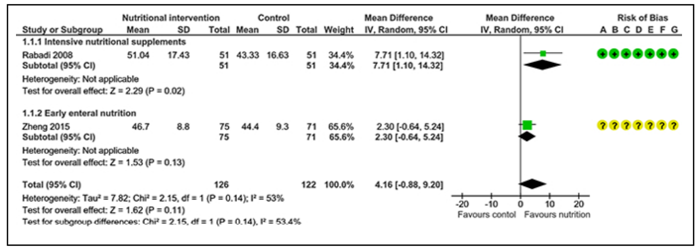
CENTRAL, Cochrane Central Register of Controlled Trials; ICTRP, World Health Organization International Clinical Trials Registry Platform

Experimental interventions

There were 4 types of nutrition therapy. In 3 trials (4, 23, 27), the experimental group received oral nutritional supplements for energy and protein. Two trials (28, 29) provided essential amino acids (EAAs) to the experimental groups; 2 trials (24, 25) provided early enteral nutrition (1 trial (25) used supplements with high nutritional content; another trial (24) did not specify the intervention); 1 trial (26) provided individualized nutritional care, in which participants were given energy and protein rich feedings by mouth or enteral tube if they did not meet nutritional requirements. Supplementary Table S1 shows the experimental and control interventions in each trial.

Figure 2

Forest plot of comparison, nutritional interventions versus control for ADL



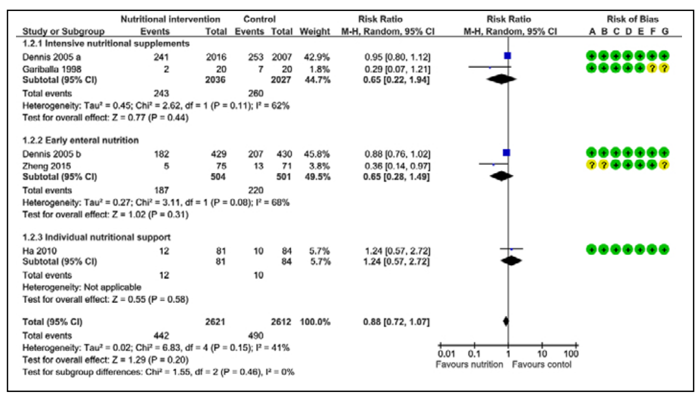
A: Random sequence generation (selection bias). B: Allocation concealment (selection bias). C: Blinding of participants and personnel (performance bias). D: Blinding of outcome assessment (detection bias). E: Incomplete outcome data (attrition bias). F: Selective reporting (reporting bias), G: Other bias. CI, indicates confidence interval; IV, inverse variance; SD, standard deviation

Co-intervention on rehabilitation therapy

Among all the trials, 1 trial (28) described therapeutic exercises. In this trial, rehabilitation included passive, active, and active-assistive range-of-motion exercises, coordination and facilitation techniques for the contralateral limbs, trunk exercises, active exercises of the unaffected limbs, and ambulation with assistive devices or support.

Figure 3

Forest plot of comparison, nutritional interventions versus control for all-cause mortality



A: Random sequence generation (selection bias). B: Allocation concealment (selection bias). C: Blinding of participants and personnel (performance bias). D: Blinding of outcome assessment (detection bias). E: Incomplete outcome data (attrition bias). F: Selective reporting (reporting bias), G: Other bias. CI, indicates confidence interval; M-H, Mantel–Haenszel

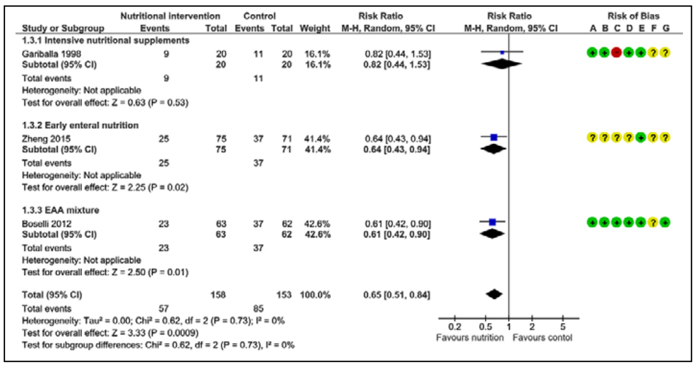
Risk of bias in included studies

Based on the information that we collected from the published trials and information from authors, we rated many trials as having a high or unclear risk of bias for each outcome. We determined that the risk of bias in allocation domain was low in 7 trials and 1 trial (25) was indeterminate due to insufficient information. As for the blinding domain for participants and personnel, we found that 4 trials (4, 23, 24, 26) had a high risk of bias and 1 trial (25) had an unclear risk of bias. In the blinding domain for outcome assessors, 2 trials

(23, 26) had a high risk of bias and 2 (24, 25) had an unclear risk. As for the incomplete outcome data domain, all trials, except 1 (25) with an unclear risk, had a low risk of bias. For the selective outcome reporting domain, 4 trials (4, 25, 28, 29) were deemed to have an unclear risk because the protocols were not available. A low risk of bias was found in the domain of other potential sources of bias for all trials except 1 (25) that had an unclear risk. The risks of bias for each trial are shown in the figures on meta-analyses for each outcome (Figures 2–5 and Supplementary Figures).

Figure 4

Forest plot of comparison, nutritional interventions versus control for infections



A: Random sequence generation (selection bias). B: Allocation concealment (selection bias). C: Blinding of participants and personnel (performance bias). D: Blinding of outcome assessment (detection bias). E: Incomplete outcome data (attrition bias). F: Selective reporting (reporting bias), G: Other bias. CI, indicates confidence interval; M-H, Mantel–Haenszel; EAA, essential amino acids.

Adverse events due to nutrition therapy

No studies reported adverse events due to nutrition therapy.

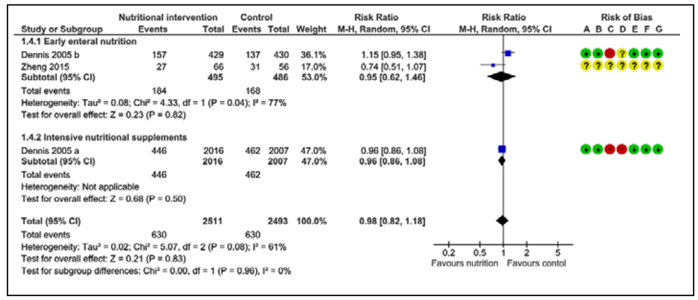
Results of meta-analysis

ADL

Data on ADL were reported in 5 of the trials (4, 25, 27-29). Of these trials, 3 used FIM for the assessment (27-29) and 2 used BI (4, 25). The meta-analysis was conducted using 2 of these 5 trials (25, 27). The reasons that 3 of the 5 trials could not be used in the meta-analysis were that 1 trial (4) reported BI scores as medians and 2 trials (28, 29) reported only the total FIM score. The meta-analysis showed that nutritional interventions had no significant effects on ADL (MD: 4.16; 95% CI -0.88 to 9.20; P=0.11; I^2=53%; 2 trials; 248 participants; low-quality evidence). In the assessment of quality of evidence, we rated the risk of bias domain as low quality because 1 trial weighted 65.5% in the meta-analysis of ADL had insufficient information. In addition, we rated the imprecision domain as low quality because the number of participants included in the meta-analysis was small (Figure 2).

Figure 5

Forest plot of comparison, nutritional interventions versus control for severe disability on the modified Rankin Scale



A: Random sequence generation (selection bias). B: Allocation concealment (selection bias). C: Blinding of participants and personnel (performance bias). D: Blinding of outcome assessment (detection bias). E: Incomplete outcome data (attrition bias). F: Selective reporting (reporting bias), G: Other bias. CI, indicates confidence interval; M-H, Mantel–Haenszel

All-cause mortality

Data on all-cause mortality were reported in 5 trials (4, 23-26). The meta-analysis showed that nutritional interventions had no significant effects on all-cause mortality (RR: 0.88; 95% CI 0.72 to 1.07; P=0.20; I^2=41%; 5 trials; 5233 participants; moderate-quality evidence) (Figure 3).

Infections

Data on infections were reported in all 5 trials. The meta-analysis was performed using 3 trials (4, 25, 29) wherein the word "infection(s)" was used in the results section. In the other 2 trials (23, 24), there were some complications that could not be definitively identified as infections; thus, we did not use them for this part of the meta-analysis. We found that the nutritional interventions had a significant effect on infections (RR: 0.65; 95% CI 0.51-0.84; P<0.001; I^2=0%; 3 trials; 311 participants; low-quality evidence) (Figure 4).

Severe disability on the mRS

Data from the mRS were reported in 3 trials (23-25). The meta-analysis showed that nutritional interventions had no significant effect on the incidence of severe disability as defined by the mRS (RR: 0.98; 95% CI 0.82-1.18; P=0.83; I^2=61%; 3 trials; 5004 participants; very low-quality evidence) (Figure 5).

Incidence of pneumonia

The incidence of pneumonia was reported in 4 trials (23-25, 29). The meta-analysis showed no significant effect of nutritional intervention on pneumonia (RR: 1.01; 95% CI 0.87-1.18; P=0.87; I^2=0%; 4 trials; 5143 participants; low-quality evidence) (Supplementary Figure S1).

Walking ability

The data of walking ability was reported in 1 trial (27). Thus, we could not perform a meta-analysis on this outcome. Walking ability was assessed using distance in a 2-min walk test and a 6-min walk test. In both of these outcome measures, the experimental groups had significant improvements in walking distance (Supplementary Figures S2 and S3).

Fall

There were no trials that used incidence of fall as an outcome measure.

Stroke recurrence

Data on stroke recurrence were reported in 2 trials (23, 24). The meta-analysis showed that nutritional interventions had no significant effect on stroke recurrence (RR: 0.92; 95% CI 0.53-1.59; P=0.76; I^2=55%; 2 trials; 4872 participants; low-quality evidence) (Supplementary Figure S4).

Quality of life

Data on QOL were reported in 3 trials. These trials used the EUROQoL and reported median values. Thus, we could not perform a meta-analysis on the data. Among them, 2 trials (23, 24) reported no significant difference in improvement of QOL between the experimental and control groups. On the other hand, 1 trial (26) reported that the intervention group had a significant improvement in functional mobility, self-care, and usual activities, while pain/discomfort and anxiety/depression were not significant. In this trial, the experimental group had a significant 20% increase in EUROQoL scores after 3 months.

Discussion

Summary of results

We included 8 trials randomizing 5484 participants. Meta-analyses were possible for ADL, all-cause mortality, infections, severe disability on the mRS, incidence of pneumonia and stroke recurrence. In the present review, there was no significant effect of nutrition therapy on ADL. Conversely, nutrition therapy had a possible effect on decreasing infections. The findings in the present review should be interpreted with caution as the quality of the evidence ranged from moderate to very low, depending on the outcome measure. All outcomes were measured in a small number of trials. The meta-analysis for ADL as a primary outcome was performed with only 2 trials with a small number of participants. Until there are more large trials of high methodological quality, using similar interventions in similar participants, the effect of nutrition therapy on rehabilitation outcomes would remain unclear.

Overall completeness and applicability of evidence

The trials identified for this review represent certain interventions and participant characteristics. There were 4 interventions used: intensive nutritional supplementation, early enteral nutrition, EAA supplementation, and individual nutrition support. The participants had acute stroke, sub-acute stroke, or chronic stroke. Many of them had acute stroke, and few trials had sub-acute or chronic stroke patients. In addition, the nutritional status of included participants was not limited to "possible malnutrition." Malnutrition can contribute to functional decline (12); thus, trials with malnourished participants may result in better outcomes of nutrition therapy. However, this is uncertain based on the few trials in the present review. The effectiveness of combination of resistance exercise and protein supplementation on physical function has been reported in older adults (30). Though the present review had insufficient information on therapeutic exercises, the type of exercises may be important when combined with nutrition therapy. Finally, we found no reports of adverse events from nutrition therapy in the studies we reviewed. Most trials excluded patients with digestive organ problems, heart failure, or terminal illness. Thus, nutrition therapy can be assumed to be generally safe in patients without these conditions.

Potential biases in the review process

We included trials regardless of publication type, publication status, date and language. We contacted relevant authors for additional information when the need arose. We conducted the review using the methods recommended by Cochrane. We followed a protocol developed prior to undertaking the review, though we made a small change to this protocol once the review began. In our protocol, we defined trial participants as over 65 years old. However, we selected trials in which the participants' mean age was over 65 years because all the trials had no restriction on age. In addition, we initially interpreted mRS as an index for ADL in our protocol, but we subsequently used mRS as an independent indicator of disability level, separate from ADL. Because mRS, unlike BI and FIM, is based on broad categories, it could introduce inaccuracies into the meta-analysis of ADL.

Consistencies and inconsistencies with other reviews

There have been two systematic reviews of the effects of nutrition therapy in stroke patients (17, 18). One review focused on patients with dysphagia after stroke (18). There was no significant difference between the experimental and control groups in the outcomes of death or dependency. This finding is consistent with the present review. Another review documented the effect of nutritional support in hospitalized adults at nutritional risk (17). In a sub-group analysis of stroke patients, nutritional support had no significant effect on all-cause mortality, as in the present study. As for the effect on morbidity, which included infections, there was a significant benefit, though it was for all patients including stroke patients. Also in the present study, nutrition therapy had a significant association with decreased infections. Thus, nutrition therapy might reduce the risk of infections in older stroke patients undergoing rehabilitation. Regarding pneumonia, the present review found no significant benefit or harm from nutrition therapy, as with the previous review (17). One review described a possible benefit of nutrition therapy on recovery of neurocognitive function in ischemic stroke patients (14).

However, since that review was not systematic, we cannot compare the results with our current study.

Conclusions

We found that nutrition therapy had no statistically significant effects on ADL in older stroke patients undergoing rehabilitation, and the studies reviewed presented a low quality of evidence. In contrast, nutrition therapy had a significant benefit in reducing infections. Limitations of this study were the small number of trials and the lack of high quality evidence. Trials with high-quality methodology, similar subjects, and similar interventions are warranted to determine the effect of nutrition therapy in older stroke patients undergoing rehabilitation.

Conflict of interest: None declared.

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