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Original Paper

Comparative efficacy of swallowing therapies for dysphagia to prevent pneumonia in patients with acute or subacute stroke: A network meta-analysis of randomized controlled trials

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Abstract

Pneumonia is a frequent complication in patients with acute and subacute stroke. Hence, pneumonia prevention is a prominent issue. Although previous reports have demonstrated the efficacy of various swallowing therapies in preventing pneumonia, details of their efficacy profiles have not been fully elucidated. This study aimed to compare the effectiveness of behavior interventions (BI), metoclopramide (MCP), prophylactic antibiotics (PA), and pharyngeal electrical stimulation (PES) in preventing pneumonia between patients with acute to subacute stroke and a control group (N). A network meta-analysis of randomized controlled trials was conducted. The primary endpoint was the frequency of pneumonia. Integrated estimates were expressed as odds ratios (ORs) and 95% credible intervals (CIs). Five studies (n=1,179) were included in the analysis. The frequency of pneumonia was significantly lower in group MCP than in groups BI, PA, and N (OR [95% CI] of MCP vs. BI, PA vs. MCP, and MCP vs. N: 0.127 [0.018 to 0.450], 24.15 [3.653 to 84.50], and 0.081 [0.013 to 0.273], respectively). There was no significant difference in the frequency of pneumonia between each treatment pair among the BI, PA, PES, and N groups. MCP showed good pneumonia prophylaxis in patients with acute to subacute stroke compared to BI or PA. Further clinical studies to verify the efficacy and safety profile of MCP in preventing pneumonia are warranted.

Key words: pneumonia, swallowing therapy, network meta-analysis

Introduction

Pneumonia is a major complication of acute stroke[1-3]. The incidence of stroke-related pneumonia ranges from 20% to 60%, depending on the patient population and the choice of diagnostic criteria[1,4,5]. The main causes of post-stroke pneumonia are dysphagia and subsequent aspiration[2,5,6]. Immunosuppression due to stroke also plays a significant role in the development of post-stroke pneumonia[3,4]. In addition to oropharyngeal dysfunction, stroke can cause lower esophageal sphincter and stomach dysfunction, resulting in symptoms such as gastric insufficiency paralysis, increased residual volume, decreased lower esophageal sphincter closing pressure, and gastroesophageal reflux[4,5,7,8]. These dysfunctions are caused by early nerve damage and circulating stress hormones, such as adrenaline and dopamine, which affect gastric motility[8].

Pneumonia is a clinical problem for patients with acute and subacute stroke as it affects the prognosis of these patients. Therefore, preventing pneumonia is a prominent issue in stroke management[7].

Several reports have examined the effectiveness of various swallowing therapies, including behavior intervention (BI), metoclopramide (MCP),

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prophylactic antibiotics (PA), and pharyngeal electrical stimulation (PES), in preventing pneumonia, but details of their efficacy profiles have not been fully elucidated to date[9]. By using the statistical method of network meta-analysis (NMA), not only can the effects of multiple intervention groups be compared simultaneously, but indirect comparisons can also be made to estimate an integrated effect size of factors that have not been previously evaluated. However, heterogeneity and inconsistency among the included studies must be considered when interpreting the results of the NMA.

Therefore, this study aimed to compare the effectiveness BI, MCP, PA, and PES in preventing pneumonia between patients with acute to subacute stroke groups and a control group (N) using an NMA of randomized controlled trials (RCTs).

Materials and methods

1. Literature search

Relevant literature were extracted from the literature reported in the Cochrane database[9].

2. Patients

Patients with acute or subacute stroke and admitted to an intensive care unit or higher care unit were included in this study.

3. Intervention / comparison

It was a requirement for inclusion in this analysis that one of the following treatment groups be included in the treatment comparison group other than treatment group of BI, MCP, PA, PES, and N.

4. Outcome

The primary endpoint was the incidence of pneumonia, and the effect size was expressed as the odds ratio (OR) and 95% credible intervals (CIs).

5. Study design

The study was a randomized, parallel, controlled trial.

6. Statistical analysis method of NMA

Bayesian NMA[10-12] was performed according to a robustly established method developed by the National Institute of Health, employing the standard Bayesian model described by Dias *et al.*[13-15] and assuming disagreement and heterogeneity among the included studies. A non-informative prior distribution was applied, and Gibbs sampling was used to evaluate the posterior distribution of effect sizes based on the Markov chain Monte Carlo method[11, 16]. The number of iterations was set at 50,000, and the first 10,000 iterations were used as a burn-in sample to eliminate the effect of the initial values. The effect size was expressed as OR (mean of the posterior distribution) and its 95% CI, and the difference in effect size between treatment groups for each endpoint was considered significant if the 95% CI did not include 1. Convergent diagnosis was also performed for all comparisons using the Brooks–Gelman–Rubin (BGR) diagnostic method[16, 17]. Both visual and BGR diagnostics were used to verify the convergence of the models. OpenBUGS 1.4.0 (MRC Biostatistics Unit, Cambridge Public Health Research Institute, Cambridge, UK) was used for the analysis.

Results

1. Literature search

From the previous literature reported in the Cochrane database, five studies (n=1,179) were included in this analysis[18-22]. The characteristics of the included studies are shown in Table 1. The key inclusion criteria of the study participants for each study are shown in Table 2. Two studies[20, 22] compared BI with N, and one study each compared MCP with N[18], PA with N[19], and PES with N[21]. For categorization of the treatment arms in each included study, we followed those of previous reports[9].

2. Primary endpoint : incidence of pneumonia

The frequency of pneumonia was significantly lower in group MCP than in groups BI, PA, and N (OR [95% CI] of MCP vs. BI, PA vs. MCP, and MCP vs. N : 0.127 [0.018 to 0.450], 24.15 [3.653 to 84.50], and 0.081 [0.013 to 0.273], respectively). There was no significant difference in the frequency of pneumonia between each treatment pair among the BI, PA, PES, and N groups (Figure 1).

3. Bias assessment

In this study, patients with acute to subacute stroke were included. Among the five studies evaluated, one study[20] included patients who were followed up to 6 months after stoke onset. To address this conceptual heterogeneity, we performed a sensitivity analysis that excluded the literature[20]. The results are shown in Table 3. The results of the sensitivity analysis showed no change in the statistical significance in each pair of treatment comparisons. Therefore, we concluded that the inclusion / exclusion of Reference 20 did not

Table 1. Characteristics of the included studies

Study name	Study design	Treatment arms	Details of interventions	N	Age-yr mean (SD)	Female No. (%)	Pathology	Chest infection or pneumonia No. (%)
Carnaby 2006	RCT (3 arms)	UC + DSE + ADM (High intensity)	Direct swallowing exercises (e.g., effortful swallowing, supraglottic swallow technique) and appropriate dietary modification added on UC	102	69.8 (12.5)	42 (41)	Infarction 93 (91) hemorrhage 8 (8) unknown 1 (1)	28 (27)
		UC + SCS (Low intensity)	Swallowing compensation strategies, mainly environmental modification; safe swallowing advice; and appropriate dietary modification added on UC	102	72 (12.4)	43 (42)	Infarction 90 (88) hemorrhage 10 (10) unknown 2 (2)	26 (25)
		UC	Patient management by the attending physician as per usual practice	102	71.4 (12.7)	43 (42)	Infarction 90 (88) hemorrhage 11 (11) unknown 1 (1)	48 (47)
				306/total				
Jayasekeran 2010	RCT (2 arms)	PES	Pharyngeal electrical stimuli (0.2-ms pulses, 280 V) were delivered at a set frequency (5 Hz), intensity (75% of maximum tolerated), and duration (10 minutes)	16	75 (2.7)*	NR	Infarction 15 (94) hemorrhage 1 (6)	2 (13)
		Sham	Sham	12	74 (2.3)*	NR	Infarction 11 (92) hemorrhage 1 (8)	3 (19)
				28/total				
Kang 2012	RCT (2 arms)	BET added on CST	Bedside exercise training, which consisted of oral, pharyngeal, laryngeal, and respiratory exercises through the nursing intervention added to CST	25	68.3 (6.6)	9 (36)	Infarction 15 (60) hemorrhage 10 (40)	5 (20)
		CST	Conventional swallowing therapy	25	66.7 (6.01)	7 (28)	Infarction 17 (68) hemorrhage 8 (32)	6 (24)
				50/total				
Warusevitane 2014	RCT (2 arms)	MCP 10 mg (21days)	Metoclopramide 10 mg via a nasogastric tube for 21 days or until nasogastric feeds were discontinued	30	76.9 (6.3)	19 (63)	Infarction 29 (97) hemorrhage 1 (3)	8 (27)
		Placebo (21days)	Placebo 3× daily via a nasogastric tube for 21 days or until nasogastric feeds were discontinued	30	79.2 (10.8)	19 (63)	Infarction 27 (90) hemorrhage 3 (10)	26 (87)
				60/total				
Kalra 2015	RCT (2 arms)	Antibiotics (7 days)	Antibiotic chosen at intervention centers conformed to local antibiotic policy added on recommended care for dysphagia	339	77.7 (11.9)	347 (56.5)	Ischemic 546 (89) hemorrhagic 69 (11) Missing data 0 (0)	56 (17)
		Control (7 days)	Recommended care for dysphagia	396	78.0 (12.2)	343 (56.8)	Ischemic 545 (91) hemorrhagic 56 (9) Missing data 1 (0.2)	56 (14)
				735/total				

*; mean (standard error of the mean); N, number of patients; yr, year; No., Number of applicable patients; RCT, randomized controlled trials; UC, usual care; SCS, swallowing compensation strategies; DSE, direct swallowing exercises ADM, appropriate dietary modification; PES, pharyngeal electrical stimulation; NR, not reported; BET, bedside exercise training; CST, Conventional swallowing therapy; MCP, metoclopramide.

Table 2. Key inclusion criteria

Study names	Key inclusion criteria
Carnaby 2006	Patients in whom a clinical diagnosis of stroke was confirmed by the attending clinician (GJH), according to the WHO definition of stroke, and consented for study inclusion within 7 days of stroke onset
Jayasekeran 2010	Patients admitted with an index stroke and prospectively screened for swallowing disability
Kang 2012	Patients who had an onset of stroke within 6 months; whose dysphagia was confirmed by VFSS
Warusevitane 2014	Patients within 7 days of acute ischemic or hemorrhagic stroke confirmed by computed tomographic scan of the brain who required nasogastric feeding for >24 hours and could be recruited within 48 hours of NGT insertion
Kalra 2015	Patients who were older than 18 years, had a confirmed diagnosis of new stroke (ischemic or hemorrhagic) with onset of symptoms within 48 h at recruitment, and in whom swallowing was unsafe because of impaired consciousness, failed the bedside swallow test, or presence of a nasogastric tube

WHO, World Health Organization; VFSS, videofluoroscopic swallowing study; NGT, nasogastric tube

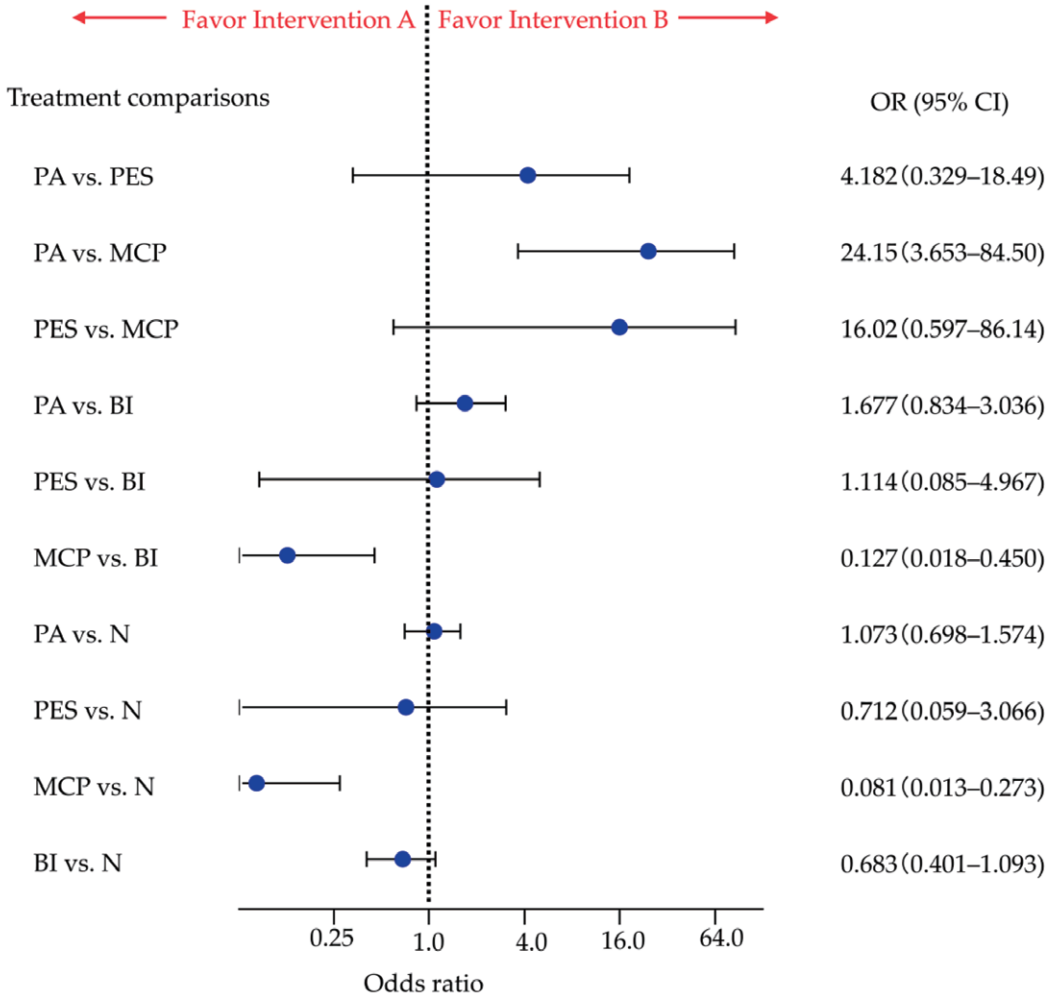

Fig. 1. Comparison of pneumonia prevention efficacy among the five swallowing treatment groups (BI, MCP, PA, PES, and N). Data are expressed as odds ratios and 95% confidence intervals. Treatment comparisons are expressed as intervention A vs. intervention B; BI, behavior intervention; MCP, metoclopramide; PA, prophylactic antibiotics; PES, pharyngeal electrical stimulation; N, control; OR, odds ratio; CI, confidence interval.

affect the conclusion of this analysis.

In addition, we assessed the statistical heterogeneity of the study groups[20, 22] that compared the same treatment groups. The results did not show any significant statistical heterogeneity (p=0.143).

In this analysis, we were not able to statistically assess for inconsistency because the comparison between any of the two treatment groups was either direct or indirect only. Hence, we could not evaluate the difference between the integrated effect sizes of the direct and indirect comparisons. Therefore, the possibility of the existence of inconsistency in this NMA could not be completely excluded.

Table 3. Results of sensitivity analysis

Treatment comparisons	OR (95% CI)
PA vs. PES	4.182 (0.329–18.49)
PA vs. MCP	24.15 (3.653–84.50)
PES vs. MCP	16.02 (0.597–86.14)
PA vs. BI	1.736 (0.832–3.223)
PES vs. BI	1.153 (0.086–5.164)
MCP vs. BI	0.131 (0.019–0.470)
PA vs. N	1.073 (0.698–1.574)
PES vs. N	0.712 (0.059–3.066)
MCP vs. N	0.081 (0.013–0.273)
BI vs. N	0.667 (0.375–1.105)

Table 3. Results of sensitivity analysis performed by excluding reference 20. Comparison of pneumonia prevention efficacy among the five swallowing therapies (BI, MCP, PA, PES, and N). Data are expressed as OR and 95% CI; BI, behavior intervention; MCP, metoclopramide; PA, prophylactic antibiotics; PES, pharyngeal electrical stimulation; N, control; OR, odds ratio; CI, confidence interval.

Discussion

This study compared the efficacy of BI, MCP, PA, PES, and N in patients with acute and subacute stroke. The results showed that MCP had a better effect in preventing pneumonia than BI, PA, and N.

Previous reports have shown that MCP is more effective than N in preventing pneumonia[18]. However, there have been no previous reports comparing the efficacy of MCP with various swallowing therapies in preventing pneumonia. This study is the first to compare the efficacy of MCP with other swallowing therapies in preventing pneumonia. The results suggest that MCP is significantly better in preventing pneumonia than BI or PA.

There may be physiological and bioscientific explanations for the favorable pneumonia-preventive effect of MCP compared with other swallowing treatments. First, MCP, a potent antiemetic, reduces vomiting, which subsequently reduces the risk of aspiration. MCP also increases lower gastroesophageal sphincter tone and promotes gastric emptying through D2 receptor antagonism, thus reducing the risk of gastroesophageal reflux. In other words, the prevention of reflux and associated silent aspiration may lead to a reduction in the frequency of pneumonia in patients treated with MCP[23, 24]. Furthermore, stroke patients treated with MCP were reported to have earlier improvements in swallowing, resulting in an early resumption of oral feeding[23–26]. This leads to the reactivation of the swallowing center, which contributes to the prevention of pneumonia. These properties of MCP may explain, at least partially, its pneumonia-preventive effect. Further verification of the mechanisms underlying the effects of MCP is needed.

This does not necessarily mean that MCP is recommended for all patients. For example, the use of MCP in patients with extrapyramidal symptoms or ileus should be carefully considered. Furthermore, the results of this study do not negate the effectiveness of other swallowing therapies, such as BI, in patients with acute to subacute stroke. This is because some reports have suggested that BI may also be effective in improving swallowing in these patient groups[20]. Although reports have suggested that some BIs are effective in preventing pneumonia, further verification is needed to determine these types of BIs[22]. In addition, the choice of swallowing therapies discussed in this analysis should be made in consideration of the patient's background. Further clinical studies are needed to determine which swallowing therapy is the most effective in preventing pneumonia in which patients.

This study has its limitations. The results of the sensitivity analysis were similar to the main analysis, and the statistical assessment of heterogeneity did not show significant heterogeneity. Nevertheless, we still cannot completely exclude the possibility that there was non-negligible background heterogeneity, which could have influenced the results. Furthermore, the analytical model of this NMA could not evaluate statistical inconsistency (dissociation between direct and indirect comparisons). Therefore, the possibility of the existence of inconsistency could not be completely eliminated[10, 12, 27–29].

In summary, this study compared the efficacy

of swallowing therapies in preventing pneumonia in patients with acute or subacute stroke. The results showed that the incidence of pneumonia was significantly lower in the group that received MCP than in the groups that received BI or PA. These results provide useful information on acute stroke treatment.

This study is an NMA that includes direct and indirect comparisons, which need to be confirmed by a large head-to-head RCT using direct comparisons. Further studies are necessary to provide information on patient background factors that predict the efficacy of each swallowing therapy for pneumonia prevention.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Institutional review board statement

This clinical study was a systematic review and meta-analysis and used only previously published, de-identified patient data. Therefore, institutional review board approval was waived.

Informed consent statement

Due to the retrospective nature of this study and being a systematic data review and meta-analysis, written patient consent was waived.

Data availability statement

The authors confirm that the data sets analyzed in the present study are available from the corresponding author upon reasonable request.

Trial registry

UMIN Clinical Trials Registry : UMIN000045215.

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