EFFICACY AND SAFETY OF METOCLOPROMIDE TO PREVENT ASPIRATION PNEUMONIA IN PATIENTS WITH STROKE FED BY NASOGASTRIC TUBES: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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Abstract

Background: Post stroke pneumonia is a major cause of mortality and morbidity in patients with stroke fed via Nasogastric Tubes (NGT). Metoclopromide, a prokinetic agent, has been recommended to reduce incidence of aspiration pneumonia, but its efficacy is controversial. The aim of the study was to assess whether regular treatment with Metoclopromide could safely reduce the rate of aspiration pneumonia in stroke patients fed by NGT.

Materials and methods: This double blind randomized placebo-controlled trial was carried out in Department of Neurology, Chittagong Medical College Hospital, during September 2017 to August 2018. One hundred consecutive patients admitted in Neurology ward with no signs of pneumonia within 7 days of stroke onset and 48 hours of insertion of a NGT were recruited. Consecutive eligible patients were randomly allocated to receive either Metoclopromide 10 mg or placebo thrice daily via NGT for maximum 7 days or until NG feeds were discontinued whichever was earlier. Clinical signs of aspiration pneumonia were recorded daily. On 21st day after recruitment patients' health and the level of recovery was reviewed by Modified Rankin Scale (MRS) and recorded.

Results: One hundred patients [Mean age, 60.88 (±13.99) years, 36 men and 64 women] were randomized in a 1:1 ratio. Both the groups were similar in terms of baseline characteristics. Patients treated with Metoclopromide was 3.71 times more likely have no pneumonic episodes during their 7 days of treatment compared to placebo group. Regarding number of aspiration episodes 3.16 times more aspiration were noticed in placebo group compared to Metoclopromide group. The adjusted mean differences of number of antibiotic days and MRS score at day 21 were also significantly more in placebo group than Metoclopromide group. However, mortality at 21 days was similar in two groups. Diarrhoea was the only observed adverse event with similar distribution in both groups.

Conclusion: This study confirmed that Metoclopromide may reduce the risk of aspiration pneumonia in stroke patients receiving nasogastric tube feeds.

Key words : Metoclopromide; Stroke; Pneumonia.

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Introduction

Stroke is the second leading cause of death worldwide among 240 causes, after ischaemic heart disease, and it is projected to remain so by 2030.[1,2] World Health Organization ranks mortality due to stroke in Bangladesh as number 84 in the world in 2011 and in 2017 the rank changed to 34 in the world.[3,4] Pneumonia is one of the most common medical complications following acute stroke affecting 14% of patients.[5] Post-stroke pneumonia was significantly associated with development of several nonpneumonia medical complications (Such as gastrointestinal bleeding, decubitus ulcer, deep vein thrombosis, epileptic seizure, atrial fibrillation/flutter, urinary tract infection and recurrent stroke) after ischemic or hemorrhagic stroke.[6] So, post-stroke pneumonia is associated with increased risk of in hospital mortality, prolonged length of hospital stay, and has considerable economic impact on healthcare resources.[7] The pathophysiology of post-stroke pneumonia is multifactorial. The combination of stroke-induced immunodeficiency and aspiration of oropharyngeal secretions and gastric contents into the lungs related to impaired consciousness and dysphagia predisposes patients to post-stroke pneumonia in the first few days post stroke.[8]

Nutrition is often provided via Nasogastric Tubes (NGTs) during the early days after stroke in the presence of severe dysphagia. However, patients fed via NGTs remain at a high risk of pneumonia, with the incidence ranging from 33% to 70%.[9] Lower oesophageal sphincter dysfunction is exacerbated by the presence of an NGT, which predisposes to reflux of stomach contents and microaspiration.[10] Prevention of vomiting and regurgitation could, therefore, be an effective method to reduce pneumonia in this patient group.

In this regards Metoclopromide, a prokinetic agent would be a promising drug. A recent study of Metoclopromide in stroke patient fed via NGT showed 69% reduction in pneumonia.[11] Another study showed delayed development of pneumonia in NGT feeding patients treated with Metoclopromide.[12] However, systemic reviews and meta-analysis of RCTs using Metoclopromide for preventing nosocomial pneumonia fed via NGT revealed no definite conclusions about the application of this drug for the reduction of pneumonia.[13,14] As Metoclopromide is a low cost, available and beneficial drug and there are few evidence form clinical studies in stroke patients to show the role of Metoclopromide in preventing aspiration pneumonia in our setting, we have taken the privilege to conduct this randomized controlled trial of Metoclopromide in stroke patients fed by NGT.

Materials and methods

This double blind, placebo-controlled randomized trial was conducted in the Neurology Department of Chittagong Medical College Hospital, Chattogram, Bangladesh, from September 2017 to August 2018. Patients within 7 days of acute ischemic or hemorrhagic stroke confirmed by computed tomographic scan of the brain who required NGT feeds for >24 hours, and could be recruited within 48 hours of NGT insertion, were eligible for the study. The exclusion criteria for the study were signs and symptoms of chest infection before recruitment, a history of chronic neurodegenerative diseases that could affect swallowing (eg, Parkinson disease and motor neuron disease) oesophageal disorders, terminal illness and contraindications to Metoclopromide.[15]

Eligible participants were randomized to 10 mg Metoclopromide (10 mL) or placebo (10 mL normal saline) three times daily via the NGT. Treatments were continued until NGT was no longer necessary-because of improvement of swallowing, or withdrawal of active treatment as part of end-of-life care-or for a maximum of 7 days, which ever was earlier. The investigational product was Metoclopromide (Metocol, Opsonin Pharma Limited) supplied in pet bottle containing 100ml colorless solution in each file. Equal number of identical bottle was filled with 100 ml normal saline. Each bottle was labeled with a coded A or B. Labeling was done by an Assistant Professor of Neurology ward not involved in any other aspects of the study. Consecutive eligible study participants were randomized by stratified (By sex and stroke etiology) block randomization in a block size of two. Both the outcome assessor and the participants were blinded to the assigned group.

The primary outcome was the incidence of aspiration pneumonia in participants in each treatment group. Secondary outcomes were the episodes of aspiration, number of antibiotic days, Modified Rankin Scale (MRS) score at 21 days, adverse events and drop out in each group.[16]

Sample size calculation was performed for hypothesis testing of the difference between two proportions. Assuming proportion of subjects without pneumonia in the intervention group is 73% with 30% reduction of post stroke pneumonia rate in the intervention group at 5% level of significance with 80% power a sample size of 39 patients were required in each group.[11] However, considering lost to follow-up 50 patients in each group were finally enrolled in the study. Patients' baseline characteristics, such as age, sex, co morbidities, current medication, previous lung pathology, and severity of stroke (Glasgow Coma Scale and National Institutes for Health Stroke Scale score) were recorded. All patients have a baseline chest radiograph and baseline assessments of inflammatory markers, such as WBC count and CRP. NGT feeding was started within 48 hours of hospital admission using a 16 F (French) tube for all patients. Investigational product or placebo was administered three times daily via the NGT by the nurse administering medication. Participants received standard stroke care as per hospital protocol and amount of

nasogastric feed given each day was calculated according to the patient's calorie requirement and administered as enteral bolus feeds 2 hourly, starting in the morning after completion of personal care. Patients were positioned at ≥30° head-end elevation during feeds. The position of the NGT was confirmed regularly by the researchers. These patients were regularly observed for their neurological status, vital functions, the presence of oropharyngeal secretions, and the need for oropharyngeal suction when required, vomiting and NGT dislodgement. All patients were reviewed regularly to assess recovery of swallowing using bedside testing to determine when it was safe for oral feeds to be commenced. Participants were examined daily for signs and symptoms of aspiration pneumonia, which included a full clinical examination of the chest. Inflammatory markers, and chest radiographs were requested if there would a clinical suspicion of pneumonia. The diagnosis of pneumonia made according to the British Thoracic Society recommendations, with minor modifications[17]. All instances of pneumonia were treated according to the ward antibiotic policy. Nasogastric feeds were not interrupted during episode of aspiration pneumonia.

In addition, a full general and neurological examination of all participants was performed on days 7 or on discharge. Treatment charts were reviewed for use of antibiotics and other medications on that day. Details of every witnessed aspiration were obtained from medical records. Patients were also observed for potential side effects of Metoclopromide. Finally on day 21 all the patients were reviewed again to assess the clinical outcome of stroke by MRS. Statistical analysis was conducted on an intention-to-treat basis and missing values were imputed through last value carried forward method. Continuous variables were reported as mean values ± Standard Deviation (SD) while categorical variables were expressed as count and percentage. The statistical significance of intergroup differences was compared through Independent sample t-test for continuous data and through Chi-square or Fisher's exact test for categorical data. Bivariate analyses were performed to separately examine the association between study groups and baseline and follow-up variables. Incidence of pneumonia, antibiotic days and 21 days MRS score, were compared between groups and adjusted (For age and baseline NIHSS) estimate were calculated using a Poisson regression model. A binary regression model was applied to determine the adjusted estimates between groups for 21 days mortality after adjusting for age and baseline NIHSS score. Survival analysis was done by plotting Kaplan-Meier survival curves for analysis of cumulative events of pneumonia in time between two groups. Two-sided p value < 0.05 was considered to represent a statistically significant difference. All analyses were performed by the IBM SPSS Statistics software version 23.0.

Informed consent was obtained from competent patients before enrollment. In patients who were unable to give fully informed consent, assent was obtained from a legal representative. The study protocol was approved by the Ethical Review Committee of Chittagong Medical College (Memo number: CMC/PG/2017/358) on November 14, 2017.

Results

Out of 100 enrolled patients in the study (50 in Metoclopromide arm and 50 in placebo arm) none of them were withdrawn from the trial, assessment of the main outcome (Aspiration pneumonia) was possible in all 100 participants, but 6 patients were lost to follow-up (4 in Metoclopromide arm and 2 in placebo arm) and not available for the day 21 assessment. Baseline clinical characteristics of participants were similar in both groups with a mean age around 50 years with female predominance (Table I). Most strokes were hemorrhagic (64%) predominantly subcortical location (65%) and severe (Mean baseline NIHSS score 27.82 ± 5.12 and mean GCS core 8.76 ± 2.11).

Table I : Baseline characteristics of patients.

Parameters	Metoclopromide Group (n=50)	Placebo Group (n=50)	p value
Age (Years)	60.02 (±14.33)	61.64 (±13.19)	0.558†
Sex (Male)	18 (36.0)	18 (36.0)	1.0*
Anatomical location			
Cortical	17 (34%)	18 (36%)	0.834*
Subcortical	33 (66%)	32 (64%)	
Aetiology			
Ischemic	18 (36%)	18 (36%)	1.0*
Hemorrhage	32 (64%)	32 (64%)	
Dominant hemisphere	29 (58%)	28 (59%)	0.840†

Comorbidity			
Hypertension	49 (98%)	48 (96%)	0.558*
Diabetes mellitus	9 (18%)	7 (14%)	0.585*
Atrial fibrillation	1 (2%)	0 (0%)	1.0‡
Chronic kidney disease	0 (0%)	1 (2%)	0.430‡
Glasgow coma scale	9.26 (±2.29)	8.26 (±1.78)	0.324†
NIHSS	26.88 (±4.82)	28.76 (±5.29)	0.681†

Data are presented either as mean (±SD) or frequency (percentage) as appropriate. †: Not significant by independent sample t test, *Not significant by Chi-square test, ‡Not significant by Fischer Exact test.

Incidence of pneumonia was significantly less in Metoclopromide Group in comparison to placebo group (8% versus 32%, p=0.005) with 24% absolute reduction. Mean number of aspiration episodes were significantly higher in placebo group in comparison to Metoclopromide group (< 0.001). Though 21 days mortality rate was higher in placebo group compared to Metoclopromide group (26% versus 10%) the difference was not statistically significant (p=0.066). Days on antibiotic was significantly higher in (p=0.001) and mean MRS score was also significantly higher (p=0.001) in the placebo group compared to Metoclopromide group. Regarding dropout rate in Metoclopromide group it was 4 (8%) and 2 (4%) in placebo group and the difference was not statistically significant (p=0.442). Only a reported adverse event was diarrhoea and the prevalence was similar in both groups (Table II).

Table II : Outcomes of intervention between two groups.

Parameters	Metoclopromide Group (n=50)	Placebo Group (n=50)	p value
Incidence of pneumonia	4 (8%)	16 (32%)	0.005*
Episode of aspiration	0.14 (±0.351)	0.52 (±0.544)	<0.001†
Mortality at 21 days	6 (10%)	13 (26%)	0.066*
Antibiotic days	6.52 (±1.22)	7.52 (±1.58)	0.001†
Drop out	4 (8%)	2 (4%)	0.442‡
MRS score at day 21	4.09 (±1.19)	4.81 (0.87±)	0.001†
Adverse events[a]	7 (14%)	7 (14%)	1.0*

Data are presented either as mean (±SD) or frequency (percentage) as appropriate. †: Not significant by independent sample t test, *Not significant by Chi-square test, ‡Not significant by Fischer Exact test. [a]Only diarrhoea.

Earliest point of time of pneumonia development was day 3 in the study. In Metoclopromide group all the pneumonia events occurred within 3 to 5 days following admission and in placebo group the corresponding value was 4 to 6 days. Figure 1 shows that cumulative patients developed pneumonia was significantly higher in any point of time {Log Rank (p=0.004) Breslow (p=0.005) and Tarone-Ware (p=0.004)} in the placebo group compared to Metoclopromide group.

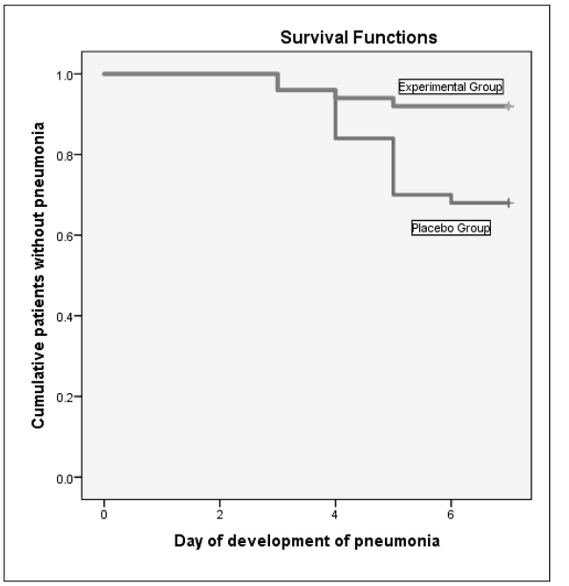

Fig 1: Cumulative patients developed pneumonia by groups in times by Kaplan-Meier survival curve.

A Poisson regression was run to predict the development of no pneumonia following stroke as well as the number of aspiration during hospital stay between two groups adjusted for age and baseline NIHSS score. Table III shows that, the rate ratio was 3.71 (95% CI:1.61-8.56), indicates that, patients treated by Metoclopromide was 3.71 times more likely have no pneumonic episodes during their 7 days of treatment compared to placebo group. Regarding number of aspiration episodes for placebo group, 3.16 (95% CI: 1.35-7.39) times

more aspiration were noticed. The adjusted mean differences of number of antibiotic days and MRS score at day 21 were also significantly more in placebo group than Metoclopromide group (p=0.002). However, after adjusting for age and baseline NIHSS score mortality at 21 days was similar in two groups (p =0.112).

Table III : Adjusted estimates of outcome parameters.

Parameters	Adjusted Estimate (95% CI)	p value
No episode of pneumonia	3.71 (1.61-8.56) *	0.002
No. of episodes of aspiration	3.16 (1.35-7.39) *	0.008
Mortality at 21 days	2.56 (0.81-8.12) †	0.112
Antibiotic days	1.01 (0.41-1.56) §	0.002
MRS score at day 21	1.88 (1.25-2.82) §	0.002

Between-group estimates are adjusted for age and baseline NIHSS score and are expressed with the placebo group as the reference group. *Rate ratio, †odds ratio and §mean difference (Placebo - Metoclopromide).

Discussion

This is one of the few randomized controlled study of Metoclopromide in patients with acute stroke fed via NGT and added to the growing body of evidence that this prokinetic agent is safe and effective to prevent pneumonia in stroke patients when fed via NGT.[11] Our findings confirm that Metoclopromide reduces the incidence of aspiration pneumonia in patients with acute stroke fed via NGT. There were fewer deaths in the Metoclopromide group than in the placebo group, but this effect was not statistically significant.

In the previous randomized controlled trials those tested Metoclopromide to prevent nosocomial pneumonia, the setting and patients were quite different from the current study.[11,12] Though Yavagal et al reported that Metoclopromide delayed the development of nosocomial pneumonia but majority of their patients were critically ill, much younger (Mean age 38.1±17.4 years) and most of them were in the postoperative phase with a wide range of complications.[12] On the other hand the other RCT conducted by Warusevitane et al was restricted to patients with stroke and all participants were breathing spontaneously similar to the current study but with a comparatively higher mean age (76.9 ±6.3 years).[11] Mean age of the current study patients were 60.88 (±13.99) years. Moreover, sample size of the current study was much higher than the previous RCT.[11]

In the current study, absolute reduction of pneumonia episode in Metoclopromide group was 24% compared to 60% in the previous study.[11] This difference was probably attributable to the difference in baseline neurological status of the patients between studies. In the current study mean NIHSS score was 27.16 compared to 18.95 in previous RCT.[11]

The mean number of episodes of pneumonia was significantly higher in the control group after adjustment of the other co-variates (Age and baseline NIHSS score). Our finding was in agreement with the findings of Warusevitane et al Similar observation was in the present study and the study of Warusevitane et al regarding higher mean number of days on antibiotic treatment in the control group than those in the Metoclopromide group.[11]

In our study, initially in bivariate analysis though there was significant reduction of mortality in treatment group in comparison to placebo group; the difference was not retained in regression analysis after adjusting for age and baseline NIHSS score (p=0.112). Similar results were also observed in other studies.[11,12] Dropout rates were similar in both groups. Patients were not able to appear in follow up evaluation probably due to financial constraints. Reluctant to come was another cause of drop out. However, these patients appeared to have better outcome on telephonic conversation.

In the current study, patients were reviewed daily for the presence of extrapyramidal reactions, but none were observed. Regarding adverse events of the intervention there were no significant differences between the two groups. Diarrhoea was the only adverse event. Other side effects like Oculogyric crises, dystonic reactions, tardive dyskinesia, and galactorrhoea were not observed, drug-induced Parkinsonism, which are well known side effects of Metoclopromide ost of which are dose dependent and reversible with discontinuation of Metoclopromide.[18-20] It is possible that limiting the maximum dose to 10 mg three times a day was safe and did not produce toxic levels that would have produced early dystonic reactions and that limiting the use of Metoclopromide to a maximum of 01 week prevented manifestation of side effects

associated with long-term use. This current study and the previous MAPS study suggested that Metoclopromide in the doses and duration used in the study seems to be safe in patient population of acute stroke.[11]

Limitations

The limitations of the present study are that it was a single center study. We could not ensure the entire NGT feeding by nursing staff. It was not possible to match age and GCS between the groups in this randomized double-blind trial although these two variables were comparable on analysis. Although the reduction in aspiration pneumonia was statistically significant, it is not possible to exclude a false positive result with confidence. It was a short term study, without long term follow-up.

Conclusions

Our study found that, Metoclopromide is effective in preventing aspiration pneumonia in patients with stroke fed by NGT and the treatment regimen is well tolerable too. In addition, the study confirmed that, regular administration of Metoclopromide for a maximum of seven days is safe in this patient group.

Recommendations

When balancing the potential fatal complications of aspiration pneumonia against potentially reversible side effects in short term use of Metoclopromide under close clinical supervision on the stroke unit is a reasonable option. These findings need to be confirmed in larger, multicentre, fully blinded randomized trials.

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Contribution of authors

MRA: Conception, designing, data collection & final approval

MAK: Data collection, drafting & final approval

MKU: Data collection, drafting & final approval

FUA: Data analysis, drafting & final approval

MHK: Data collection, critical revision & final approval

AKP: Interpritation of data, critical revision & final approval

SM: Conception, designing, critical revision & final approval

MH: Conception, interpritation of data, critical revision & final approval.

Disclosure

All the authors declared no competing interest.

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