Safety and Effect of Metoclopramide to Prevent Pneumonia in Patients With Stroke Fed via Nasogastric Tubes Trial

Anushka Warusevitane, MSc; Dumin Karunatilake, MBBS; Julius Sim, PhD; Frank Lally, PhD; Christine Roffe, MD

Background and Purpose—Pneumonia is a major cause of mortality and morbidity in patients with stroke fed via nasogastric tubes and may be because of vomiting and gastro-oesophageal regurgitation. The aim of the study was to assess whether regular treatment with metoclopramide, a D2-receptor antagonist with antiemetic and gastric prokinetic actions, could reduce the rate of aspiration and pneumonia.

Methods—Patients with no signs of pneumonia within 7 days of stroke onset and 48 hours of insertion of a nasogastric tube were recruited into a double-blind randomized placebo-controlled trial. Participants received metoclopramide 10 mg or placebo 3x daily via the nasogastric tube for 21 days or until nasogastric feeds were discontinued. Clinical signs of pneumonia were recorded daily. Pneumonia was diagnosed if the patient had relevant clinical signs, high inflammatory markers, and new infiltrates on the chest radiograph.

Results—Sixty patients (mean age, 78 years; 38 women; mean National Institutes for Health Stroke Scale score, 19.25) were randomized in a 1:1 ratio. There were significantly more episodes of pneumonia in the placebo group than in the metoclopramide group (rate ratio, 5.24; P<0.001). There were also significant differences in favor of metoclopramide in the rate of aspiration, oxygen saturation, highest inflammatory markers, and National Institutes for Health Stroke Scale. There was no significant difference in mortality between the groups.

Conclusions—This study suggests that metoclopramide may reduce the rate of pneumonia and may improve other clinical outcomes in patients with subacute stroke fed via nasogastric tube. These findings need to be confirmed in larger randomized and blinded trials.

Clinical Trial Registration—URL: https://www.clinicaltrialsregister.eu. EudraCT no: 2006-002570-22, URL: http://www.controlled-trials.com/ISRCTN18034911/18034911. (Stroke. 2015;46;00-00. DOI: 10.1161/STROKEAHA.114.006639.)

Key Words: aspirations cerebral infarction MAPS trial metoclopramide nasogastric pneumonia stroke

Pneumonia is a major complication of acute stroke. It is associated with increased mortality, morbidity, prolonged length of hospital stay, and poor rehabilitation outcomes. The incidence of stroke-related pneumonia ranges from 20% to 60%, depending on the patient population and choice of diagnostic criteria. The main causes of poststroke pneumonia are dysphagia and aspiration. In addition stroke-induced immunosuppression plays an important role in development of poststroke pneumonia. Each of the 3 stages of swallowing can be affected by stroke. In addition to oropharyngeal dysfunction, stroke also causes dysfunction of the lower oesophageal sphincter and the stomach, leading to gastroparesis, increased residual volume, reduced lower oesophageal sphincter closure pressures and gastro-oesophageal reflux. This dysfunction is partly because of the initial neurological injury and because of the circulating stress hormones, such as adrenaline and dopamine, which affect gastric motility. Oral feeding is withheld in patients with reduced levels of consciousness or with severe dysphagia to prevent aspiration. In the presence of severe dysphagia, nutrition is often provided via nasogastric tubes (NGTs) during the early days after stroke. Results of the Feed or Ordinary Diet (FOOD) trial did not show a significant survival benefit for early nasogastric feeding when compared with delayed feeding, but suggest that a policy of early commencement of tube feeding might reduce the risk of dying after stroke and that it is unlikely that
the alternative policy of avoiding early tube feeding would significantly improve survival.9 However, patients fed via NGT remain at a high risk of pneumonia, with the incidence ranging from 33% to 70%.10,11 Lower oesophageal sphincter dysfunction is exacerbated by the presence of an NGT, which predisposes to reflux of stomach contents and microaspiration.10,11 In addition, the refluxed material is frequently colonized by Gram-negative bacteria because neutral nasogastric feeds increase the pH of gastric contents and thus promote gastric colonization.11 Infected reflux adds to the bacterial burden of the already dysfunctional oropharynx, increasing the risk of microaspiration and pneumonia. Patients with stroke fed via NGT are, therefore, at high risk of aspiration pneumonia because of regurgitation of gastric contents and vomiting. Prevention of vomiting and regurgitation could, therefore, be an effective method to reduce pneumonia in this patient group.

Metoclopramide is a dopamine antagonist with both central antiemetic and gastric prokinetic effects. Centrally, it has an antagonist action on the chemoreceptor trigger zone in the medulla. In the upper gastrointestinal tract, it antagonizes dopamine D2-receptors.14 Dopamine has a direct relaxant effect on the lower oesophageal sphincter, the gastric fundus, and the antrum.14 Dopamine also inhibits the release of prokinetic acetylcholine from the cholinergic neurones of the myenteric plexus by activating prejunctional D2-receptors. By inhibiting the action of dopamine on pre- and postsynaptic D2-receptors of the upper gastrointestinal tract, metoclopramide increases the lower oesophageal sphincter pressure, gastric tone, forward peristalsis of stomach and the duodenum,14 while simultaneously decreasing pyloric sphincter pressure. These mechanisms accelerate gastric emptying, reduce gastric stasis and residual volume, and thus decrease gastrooesophageal reflux. In patients fed via NGT, this reduction in vomiting and reflux should restrict gastric contents from reaching the dysfunctional pharynx, thereby lowering the risk of aspiration and pneumonia.

The aim of this phase II trial, the Safety and Effect of Metoclopramide to Prevent Pneumonia in Stroke Patients Fed via Nasogastric Tubes (MAPS) trial, was to determine the feasibility, safety, and the potential efficacy of regular prophylactic use of metoclopramide for the prevention of pneumonia and aspiration in patients with stroke fed via NGT.

Methods

Study Design
MAPS is a randomized double-blind placebo-controlled phase II trial of regular treatment with metoclopramide versus placebo in patients with acute stroke and dysphagia fed via NGT.

Participants and Study Setting
The study was conducted on the acute stroke unit of the University Hospital of North Staffordshire, United Kingdom. Patients within 7 days of acute ischemic or hemorrhagic stroke confirmed by computed tomographic scan of the brain who required nasogastric 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 pneumonia after stroke onset, a history of chronic neurodegenerative diseases that could affect swallowing (eg, Parkinson disease and motor neuron disease), oesophageal disorders, and contraindications to metoclopramide.15 Informed consent was sought from competent patients before enrolment. In patients who were unable to give fully informed consent, assent was sought from a legal representative. The study protocol was approved by the North Staffordshire Local Research Ethics Committee (reference number 07/Q2604/41) on July 30, 2008.

Intervention
Participants were randomized to 10 mg metoclopramide (colorless solution 10 mL) or placebo (10 mL normal saline) 3× daily via the NGT. Treatment was continued until nasogastric feeding was no longer necessary—because of improvement of swallowing, insertion of a percutaneous endoscopic gastrostomy tube, or withdrawal of active treatment as part of end-of-life care—or for a maximum of 21 days, whichever was earlier.

Outcomes
The primary outcome was the number of episodes of pneumonia experienced by participants in each treatment group. Secondary outcomes were the number of episodes of witnessed aspiration in each treatment group, the highest levels of white blood cell (WBC) count and C-reactive protein (CRP) during follow-up, the lowest oxygen saturation during follow-up, the number of antibiotic days for each participant, neurological deficits (National Institutes for Health Stroke Scale [NIHSS]) at 21 days, and the final clinical outcome (swallowed improved and NGT removed: referral for percutaneous endoscopic gastrostomy; treatment withdrawn and NGT removed).

Sample Size
No formal sample size calculation was performed because we sought to recruit all eligible patients during the 3-year period available for data collection.

Randomization and Blinding
Randomization was performed for all participants using a random numbers list generated by an independent statistician at Keele University, and instructions for treatment (metoclopramide 10 mL or placebo 10 mL) were placed in opaque-sealed and numbered envelopes. All envelopes were kept in a locked cabinet in the neurosciences research office. Once informed consent had been obtained a staff member in the research office not involved in any other aspects of the trial was instructed to release the envelope with the appropriate number. This envelope, bearing the label MAPS trial drug and the participant identification number on the outside, contained the treatment instruction. The envelope was placed in the locked ward drug trolley and was only accessible to the nurse in charge of drug administration. The trial treatment was prescribed as MAPS trial drug 10 mL 3× a day via the nasogastric tube on the participant’s drug chart. The envelope was opened by the nurse dispensing drugs on the ward, who then administered the treatment as instructed. The nurse administering the study drug was not blinded to the treatment. The researcher and the medical team involved in the patients’ care were blinded to the treatment allocation.

Baseline Assessments
Patients’ baseline characteristics, such as age, sex, comorbidities, current medication, previous lung pathology, and severity of stroke (Glasgow Coma Scale and NIHSS) were recorded. All patients had a baseline chest radiograph and baseline assessments of inflammatory markers, such as WBC count and CRP.

Procedures
Unless there were good reasons to delay, NGT feeding was started within 48 hours of hospital admission using a medium bore tube with an inner diameter of 10 mm. Participants were given 10 mg metoclopramide (10 mL) or placebo (10 mL normal saline), according to the randomization, 3× daily via the NGT by the nurse administering
medication. The same type of NGT was used in all participants. All participants received standard stroke care as outlined in the Royal College of Physicians Guidelines, including physiological monitoring, early mobilization, and daily physiotherapy. The amount of nasogastric feed given each day was calculated according to the patient’s calorie requirement and administered >10 to 12 hours as continuous feeds, starting in the morning after completion of personal care. Patients were positioned at ≥30° head-end elevation during feeds. They were observed regularly during feeds, and the position of the NGT was confirmed before each feed by pH testing of gastric aspirate or, when this was too high or unobtainable, by chest radiograph. Patients had continuous cardiac monitoring and pulse oximetry during their first 3 days after stroke. These patients were managed in an observation bay close to the nurses’ station and were regularly observed for their neurological status, vital functions (6 hourly), the presence of oropharyngeal secretions, and the need for oropharyngeal suction when required, vomiting, and NGT dislodgement. An NGT that was accidentally dislodged was replaced as soon as possible, and soft mittens were applied to the nonparalyzed hand of restless patients to prevent them pulling at the tube. All patients were reviewed regularly by an independent speech and language therapist to assess recovery of swallowing using bedside testing to determine when it was safe for oral feeds to be commenced. No special swallowing therapy was performed with any of the study participants.

Participants were examined daily for signs and symptoms of pneumonia, which included a full clinical examination of the chest. Inflammatory markers, sputum cultures, and chest radiographs were requested if there was a clinical suspicion of pneumonia. The diagnosis of pneumonia was made according to the British Thoracic Society recommendations, with minor modifications (Table 1). Fulfillment of all 4 diagnostic criteria was required for the diagnosis of pneumonia. The clinical diagnosis of pneumonia and the interpretation of the chest radiographs were performed by independent clinicians. All instances of pneumonia were treated according to the hospital antibiotic policy. Nasogastric feeds were not interrupted during episodes of pneumonia.

**Table 1. Diagnostic Criteria for Pneumonia**

- Symptoms of an acute lower respiratory tract illness
- Cough
- At least one other lower respiratory tract symptom
- Tachypnoea (respiratory rate >25 per min)
- Sputum production or oropharyngeal secretions
- Hypoxia (oxygen saturation ≤80% on room air)
- New focal chest signs on examination
- New inspiratory crackles
- Bronchial breathing or
- Signs of consolidation
- At least one systemic feature
- Fever >38°C
- Symptom complex of sweating, rigors, fever, and aches and pains
- Leucocytosis (WBC >11 000 per mL)
- Leucopenia (WBC <3000 per mL)
- Elevated inflammatory marker (eg, CRP or ESR)
- No other obvious cause for the symptoms
- Radiological shadowing that is at least in 1 segment and not known to be previously present for which there is no other explanation

Table 1 was adapted from the MAPS study. Fulfillment of all 5 diagnostic criteria was required for the diagnosis of pneumonia for the MAPS study. CRP indicates C-reactive protein; and WBC, white blood cell.

In addition, a full general and neurological examination with NIHSS scoring of all participants was performed on days 4, 7, 14, and 21. Observation charts for the week were reviewed to obtain the lowest levels of oxygen saturation and the highest temperature and treatment charts were reviewed for use of antibiotics and other medications on days 7, 14, and 21. Fluid balance charts were reviewed weekly for the number of NGT days and volume of nasogastric feeds administered. Details of every witnessed aspiration were obtained from medical and nursing records. All available WBC and CRP levels during the trial period were recorded for further analysis.

Patients were also observed for potential side effects of metoclopramide. These included extrapyramidal reactions, such as dystonic reactions, including oculogyric crisis, tremors, rigidity, and tardive dyskinesia. Patients with undue drowsiness or confusion (Glasgow Coma Scale and neurological examination) had full general examination and further investigations, such as repeat head scans, blood tests, and electroencephalograms to exclude stroke-related complications before assuming these symptoms to be side effects of a medication, were recorded. Episodes of diarrhea and cardiac arrhythmias were recorded. Headache was not recorded as a side effect because it was difficult to assess in the presence of reduced level of consciousness, expressive, and receptive dysphasia and the possibility of the initial neurological damage contributing to such symptoms. Instead, the use of analgesics for >24 hours was noted. Formal testing for hyperprolactinemia was not performed.

**Statistical Analysis**

Statistical analysis was conducted on an intention-to-treat basis, and outcomes were adjusted for age and baseline NIHSS score, as pre-specified covariates. Missing values were imputed through multiple imputation, on a missing at random assumption, using 10 imputed data sets. The primary outcome, number of episodes of pneumonia, was compared between groups using a Poisson regression model, with estimates reported as rate ratios. A similar analysis was applied to the number of aspirations, but owing to zero-inflation a negative binomial regression model was applied to the number of antibiotic treatment. Mortality and final clinical outcome were analyzed using binary and multinomial logistic regression, respectively, with estimates reported as odds ratios (ORs). Follow-up NIHSS scores and lowest oxygen saturation values were analyzed using ANCOVA and reported as mean differences. Highest WBC and highest CRP did not satisfy the distributional assumptions of ANCOVA and, therefore, were first log-transformed; these estimates were expressed as fold changes.

A sensitivity analysis was performed for all outcomes by calculating unadjusted estimates. Statistical significance was set at \( P ≤ 0.05 \) (2-tailed), and 95% confidence intervals were calculated for estimates of treatment effect. Analyses were conducted in SPSS 21 (IBM Corporation, Armonk, NY) and Stata 13 (StataCorp, College Station, TX).

**Results**

Between September 2008 and September 2011, a total 2995 patients were admitted with acute stroke. Of these, 296 required nasogastric feeding. Sixty patients (20% of those fed via NGT) were recruited to the MAPS study: 30 received metoclopramide and 30 received placebo (Figure). The main reasons for exclusion were chest infections (n=202) and recruitment to another trial (n=34). None of the participants were intubated or ventilated. No participants were withdrawn from the trial, all participants were able to complete the study protocol, and assessment of the main outcome (pneumonia) was possible in all 60 participants.

Baseline clinical characteristics of participants were similar in both groups (Table 2). A wide range of ages (46–95 years) was included. Most strokes were ischemic, predominantly
anterior circulation (total anterior circulation syndrome 51/60), and severe (mean baseline NIHSS score, 19.25).

Inflammatory markers were normal on admission, confirming that participants did not have any pre-existing infections. All participants were admitted to hospital within 24 hours of stroke onset, and the NGT was inserted within 48 hours from admission. All were randomized within 24 hours of NGT insertion. Almost all patients (98%) were fed via NGT for ≥1 week, 31 patients (51%) for 2 weeks, and 19 patients (31%) for 3 weeks. There was no significant difference in the mean volume of NGT feeds between the 2 groups (Table I in the online-only Data Supplement).

All outcomes had full data except for lowest oxygen saturation, for which 10 missing values were imputed (7 in the metoclopramide group and 3 in the placebo group). All participants were admitted to hospital within 24 hours of stroke onset, and the NGT was inserted within 48 hours from admission. All were randomized within 24 hours of NGT insertion. Almost all patients (98%) were fed via NGT for ≥1 week, 31 patients (51%) for 2 weeks, and 19 patients (31%) for 3 weeks. There was no significant difference in the mean volume of NGT feeds between the 2 groups (Table I in the online-only Data Supplement).

All outcomes had full data except for lowest oxygen saturation, for which 10 missing values were imputed (7 in the metoclopramide group and 3 in the placebo group). Estimates of treatment effect for the primary outcome and for the secondary outcomes, adjusted for age and baseline NIHSS, are shown in Tables 3 and 4, respectively. Thirty-four patients experienced pneumonia (26 in the control group and 8 in the metoclopramide group), and for 94% of patients this occurred within 7 days from admission (the mean time from NGT insertion to the first episode of pneumonia was 4 days in the treatment group and 2 days in the placebo group). The mean number of episodes of pneumonia was 1.33 in the control group and 0.27 in the metoclopramide group (Table 3). From the Poisson regression, this represented a rate ratio of 5.24 (P<0.001). Table 4 shows that patients in the placebo group had a mean of 0.73 episodes of aspiration when compared with a mean of 0.03 in the metoclopramide group (rate ratio, 20.54; P=0.003). Patients in the placebo group also had a higher mean number of days on antibiotic treatment (7.57) than those in the metoclopramide group (2.27); this represented a rate ratio of 3.94 (P<0.001).

Taking treatment withdrawn and NGT removed as the reference category, patients in the placebo group were less likely than those in the metoclopramide group to have the NGT removed owing to improved swallowing (odds ratio [OR],
Table 4. Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Metoclopramide (n=30)</th>
<th>Placebo (n=30)</th>
<th>Adjusted Estimate (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of episodes of aspiration, mean (SD; range)</td>
<td>0.03 (0.18; 0.00, 1.00)</td>
<td>0.73 (0.91; 0.00, 3.00)</td>
<td>20.54 (2.75 to 153.46)*</td>
<td>0.003</td>
</tr>
<tr>
<td>Mortality at 30 days, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>8 (27)</td>
<td>12 (40)</td>
<td>1.85 (0.59 to 5.80)†</td>
<td>0.292</td>
</tr>
<tr>
<td>Alive</td>
<td>22 (73)</td>
<td>18 (60)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Highest WBC/mm³, mean (range)</td>
<td>12.23 (3.2, 23.5)</td>
<td>16.84 (4.10, 41.00)</td>
<td>1.32 (1.05 to 1.65)‡</td>
<td>0.016</td>
</tr>
<tr>
<td>Highest CRP mg/dL, mean (range)</td>
<td>60.09 (0.4, 258.0)</td>
<td>97.71 (3.50–307.00)</td>
<td>1.97 (1.15 to 3.37)‡</td>
<td>0.014</td>
</tr>
<tr>
<td>Antibiotic days, mean (SD; range)</td>
<td>2.27 (3.07; 0.00, 12.00)</td>
<td>7.57 (4.34; 0.00, 16.00)</td>
<td>3.90 (2.22 to 6.84)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS, mean (SD)</td>
<td>13.77 (8.27)</td>
<td>17.27 (9.78)</td>
<td>4.00 (1.12 to 7.89)§</td>
<td>0.043</td>
</tr>
<tr>
<td>Lowest % oxygen saturation, mean (SD)</td>
<td>93.87 (5.32)</td>
<td>85.15 (5.39)</td>
<td>−8.54 (−10.90 to −6.18)§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Final clinical outcome, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swallow improved</td>
<td>20 (67)</td>
<td>11 (36)</td>
<td>0.16 (0.03 to 0.84)†</td>
<td>0.031</td>
</tr>
<tr>
<td>Referred for PEG</td>
<td>7 (23)</td>
<td>12 (40)</td>
<td>0.81 (0.15 to 4.51)†</td>
<td>0.807</td>
</tr>
<tr>
<td>Treatment withdrawal</td>
<td>3 (10)</td>
<td>7 (23)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Clinical outcomes at 21 days after enrolment. Group-specific estimates are unadjusted. Between-group estimates are adjusted for age and baseline NIHSS score and are expressed with the placebo group as the reference group. CI indicates confidence interval; CRP, C-reactive protein; NGT, nasogastric tube; NIHSS, National Institutes for Health Stroke Scale; PEG, percutaneous endoscopic gastrostomy; and WBC, white blood cells.

*Rate ratio, †odds ratio, ‡fold change, and §mean difference (placebo–metoclopramide).

Discussion

This is the first randomized controlled study of metoclopramide in patients with acute stroke fed via NGT. The results of MAPS have shown that recruitment in the subacute stage of stroke is feasible and that regular administration of metoclopramide for a maximum of 21 days is safe in this patient group. Our findings suggest that metoclopramide reduces the incidence of pneumonia in patients with acute stroke fed via NGT. However, confirmatory evidence from a larger study is needed for the observed reduction in pneumonia. In keeping with the observed reduction in the incidence of pneumonia, the treatment group also required fewer days of antibiotics, had lower levels of inflammatory markers, and were less hypoxic. There were fewer deaths in the metoclopramide group than in the placebo group, but this effect was not statistically significant. The study also confirms that pneumonia is an early complication after stroke, with the majority occurring within the first week.18

Several pharmacological approaches to reduce pneumonia in patients with stroke with dysphagia have been described. These include agents that reduce pharyngeal colonization,19 provide antibiotic prophylaxis,20 or induce cough.21 This is the first study to assess the effect of an agent with antiemetic and prokinetic properties in the prevention of aspiration pneumonia in patients with stroke. This approach has been tested by Yagaval et al22 in an intensive care population. In a sample of 305 patients fed via NGT, regular use of metoclopramide delayed the onset of pneumonia, but did not reduce the incidence. Because pneumonia is an early complication of acute stroke and there were a significant number of patients who only required nasogastric feeds for 1 week, these few extra days of protection may be all that was required to reduce the incidence of pneumonia in the treatment group. Furthermore, there are important differences between the patient population in this study and the MAPS study. Patients in the intensive care study were much younger.
(average age, 35 years) and the majority were postoperative, with a wide range of critical illnesses. Many had further interventions associated with a high risk of reflux and aspiration, such as endotracheal intubation, mechanical ventilation, and treatment with opioids, dopamine or catecholamine agonists, which could affect peristalsis. The MAPS study was restricted to patients with stroke, and all participants were breathing spontaneously. Because the airway in this group is not protected by an endotracheal tube, regurgitation and aspiration are a greater risk. These differences in the patient populations may explain why metoclopramide prevented pneumonia in the MAPS study, but not in an intensive care population.

There are several mechanisms to explain how metoclopramide may reduce pneumonia after stroke. As a potent antiemetic, metoclopramide is expected to reduce vomiting. This was suggested in our study, where fewer episodes of vomiting and witnessed aspiration were observed in patients treated with metoclopramide. However, although vomiting is a frequent complication of cerebral hemorrhage and posterior circulation strokes, it is not common in the much more prevalent anterior circulation strokes. It is, therefore, unlikely that the antiemetic effect alone accounted for the large reduction in pneumonia seen in our study. Metoclopramide also increases the tone of the lower gastroesophageal sphincter and accelerates gastric emptying via D2-receptor antagonism, thus reducing the risk of regurgitation. As the latter is quiet, and not normally visible to the observer, its incidence and relevance may be underestimated. Transient hypoxia may be the only manifestation of aspiration of regurgitated gastric contents. It is likely that prevention of reflux and the resultant silent aspiration was responsible for the reduction in the incidence of pneumonia in patients receiving metoclopramide. Early after stroke, hypoxia is most frequent during transfers between wards, and within the head scanner. Vomiting and regurgitation caused by motion sickness could potentially explain this finding and would suggest that vomiting and regurgitation might be more common in this patient group than hitherto appreciated.

When compared with the placebo group, patients treated with metoclopramide also seemed to have better neurologic recovery and required fewer nasogastric feeds because of earlier improvement of swallowing and consequent earlier resumption of oral diet. Inflammatory activity and hypoxia have been shown to diminish penumbral recovery because of activation of tumor necrosis factor and macrophages. Swallowing has bilateral cortical representation with a dominant swallowing center that is independent of the patients’ handedness. Recovery of poststroke dysphagia depends on the take-over of control of swallowing function by the nondominant swallowing centers in the undamaged hemisphere. A reduction of pneumonia and the associated reduction in inflammation and hypoxia could have enhanced recovery of the penumbra and facilitated cortical plasticity and neurological recovery.

Most patients in the MAPS study had severe strokes, as reflected by the high mean NIHSS. Severe strokes have been shown to be associated with significant immunodepression by the activation of the hypothalamic–pituitary–adrenal axis. There is evidence from animal studies that β-blockers can improve such stroke-induced immunodepression. Antagonism of the stress hormone dopamine may have made some contribution to the observed reduction of pneumonia in patients who received metoclopramide. Another potential explanation for the reduction of pneumonia in this study is that participants may have had pre-existing gastro-oesophageal reflux. The mean age of subjects included was >70 years, and older people have a high prevalence of gastro-oesophageal reflux and hiatus hernia. Patients who are fed via NGT have a high incidence of pneumonia if there is associated reflux (43% versus 88%). Nearly half of the patients in our study were treated with proton pump inhibitors or antacids at the time of recruitment, suggesting a history of peptic ulcer disease or reflux. An NGT could have caused further disruption of the gastro-oesophageal sphincter function, which may explain the high incidence of pneumonia in the placebo group.

Extrapyramidal reactions, including dystonic reactions, tardive dyskinesia, and drug-induced Parkinsonism, are well known side effects of metoclopramide. In the MAPS study, patients were reviewed daily for the presence of extrapyramidal reactions, but none were observed. These side effects are more likely to be associated with high doses, intravenous administration, and prolonged usage. Dystonic reactions, including oculogyric crises, are most likely to occur within a few days of treatment and are more common in young patients although they have also been reported in older females. Drug-induced Parkinsonism and tardive dyskinesia are associated with long-term drug usage, usually >3 months. Tardive dyskinesia is most common in older women. Because only 30 patients were exposed to active treatment with metoclopramide in the MAPS study, we cannot exclude that such effects could occur in larger cohorts. Central nervous system side effects are easily recognized and completely reversed by stopping metoclopramide, apart from tardive dyskinesia, which may be irreversible. Other side effects, such as confusion, diarrhea, cardiac arrhythmias, and hyperprolactinemia, are fully reversible with discontinuation of metoclopramide.

It is possible that limiting the maximum dose to 10 mg 3× a day was safe and did not produce toxic levels that would have produced early dystonic reactions and that limiting the use of metoclopramide to a maximum of 3 weeks prevented manifestation of side effects associated with long-term use. Our findings suggest that metoclopramide in the doses and duration used in the MAPS trial seems to be safely used in this patient population. A much larger study is needed to exclude rare side effects. When balancing the potential fatal complication of pneumonia against potentially reversible side effects in short-term usage, time-limited use of metoclopramide under close clinical supervision on the stroke unit is a reasonable option.

The MAPS study has also shown that testing the effects of metoclopramide in this patient population was feasible because it was possible to obtain consent, randomize, and to complete observations, investigations, and follow-up of participants without major impediment and because there was a good adherence to the allocated treatment. However, 80% of patients who had NGTs were not eligible for recruitment, mainly because they already had signs of pneumonia. Early recruitment within a few hours of admission in patients who are likely to need NGT feeding (severe strokes, reduced...
level of consciousness) would allow more potentially eligible patients to be recruited.

Our study has limitations. This is a small study. No formal sample size calculation was performed. Although the reduction in pneumonia was highly statistically significant, it is not possible to exclude a false-positive result with confidence. The study was not fully blinded because the nurse dispensing the treatment was aware of the allocation. This could have introduced bias, but because the nurses were not involved in recruitment or assessment of patients this risk is considered low. A larger fully blinded randomized controlled study is needed to confirm the reduction of pneumonia and to determine whether metoclopramide affects mortality and long-term handicap.

Conclusions

The MAPS study suggests that time-limited prophylactic use of metoclopramide in patients fed via NGT is well tolerated and has the potential to reduce the rate of pneumonia and improve other clinical outcomes in patients with acute stroke fed via NGTs. These findings need to be confirmed in larger, multicentre, randomized, and blinded trials. If confirmed, the findings could lead to a new approach to the prevention of pneumonia in patients with stroke fed via NGTs.

Acknowledgments

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Disclosures

None.

References

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## SUPPLEMENTAL MATERIAL

**Supplemental Tables**

### Supplemental Table I. Average nasogastric feeding volumes (l/day)

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Treatment group</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Mean (SD)</td>
<td>1.06 (0.19)</td>
<td>1.05 (0.18)</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Week 2</td>
<td>Mean (SD)</td>
<td>1.12 (0.16)</td>
<td>0.99 (0.25)</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Week 3</td>
<td>Mean (SD)</td>
<td>1.03 (0.29)</td>
<td>1.09 (0.20)</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

### Supplemental Table II. Side effects

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Treatment group</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea; n (%)</td>
<td>6 (20)</td>
<td>9 (30)</td>
<td>0.371</td>
</tr>
<tr>
<td>Arrhythmia (New AF); n (%)</td>
<td>3 (10)</td>
<td>3 (10)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cardiac conduction abnormalities; n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Dystonic reactions; n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Oculogyris crisis; n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Tardive dyskinesia; n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Drowsiness/confusion/neurological deterioration with organic cause (CT/EEG/presence of infection); n (%)</td>
<td>8 (27)</td>
<td>4 (13)</td>
<td>0.197</td>
</tr>
<tr>
<td>Unexplained drowsiness/confusion; n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Use of analgesics &gt;24 hours; n (%)</td>
<td>4 (13)</td>
<td>1 (3)</td>
<td>0.161</td>
</tr>
<tr>
<td>Observed/reported galactorrhoea; n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Safety and Effect of Metoclopramide to Prevent Pneumonia in Patients With Stroke Fed via Nasogastric Tubes Trial

Anushka Warusevitane, MSc; Durnin Karunatilake, MBBS; Julius Sim, PhD; Frank Lally, PhD; Christine Roffe, MD

(Stroke. 2015;46:454-460.)

Key Words: aspirations • cerebral infarction • MAPS trial • metoclopramide • nasogastric • pneumonia • stroke

Abstract 10

Metoclopramide의 안전성과 효과

Cerebral infarction

Metoclopramide

PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; and TACS, total anterior circulation syndrome.

Table 3. Episodes of Pneumonia

<table>
<thead>
<tr>
<th></th>
<th>Metoclopramide (n=30)</th>
<th>Placebo (n=30)</th>
<th>Adjusted Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of episodes of pneumonia, n (%)</td>
<td>0 22 (73) 4 (13) 5.24 (2.43–11.27) &lt;0.001</td>
<td>1 8 (27) 13 (43) ... ...</td>
<td>2 0 (0) 12 (40) ... ...</td>
<td>3 0 (0) 1 (4) ... ...</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.27 (0.45) 1.33 (0.76) ... ...</td>
<td>... ...</td>
<td>... ...</td>
<td>... ...</td>
</tr>
</tbody>
</table>

Group-specific estimates are unadjusted. The between-group rate ratio is adjusted for age and baseline National Institutes for Health Stroke Scale score and is expressed with the placebo group as the reference group. CI indicates confidence interval.

Figure. Consort diagram. NG indicates nasogastric.
Table 4. Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Metoclopramide (n=30)</th>
<th>Placebo (n=30)</th>
<th>Adjusted Estimate (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of episodes of aspiration, mean (SD; range)</td>
<td>0.03 (0.18; 0.00, 1.00)</td>
<td>0.73 (0.91; 0.00, 3.00)</td>
<td>20.54 (2.75 to 153.46)*</td>
<td>0.003</td>
</tr>
<tr>
<td>Mortality at 30 days, n (%)</td>
<td>Dead</td>
<td>Alive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (27)</td>
<td>12 (40)</td>
<td>1.85 (0.59 to 5.80)†</td>
<td>0.292</td>
</tr>
<tr>
<td></td>
<td>Highest WBC/mm³, mean (range)</td>
<td>12.23 (3.2, 23.5)</td>
<td>16.84 (4.10, 41.00)</td>
<td>1.32 (1.05 to 1.65)‡</td>
</tr>
<tr>
<td></td>
<td>Highest CRP mg/DL, mean (range)</td>
<td>60.09 (0.4, 258.0)</td>
<td>97.71 (3.50–307.00)</td>
<td>1.97 (1.15 to 3.37)‡</td>
</tr>
<tr>
<td></td>
<td>Antibiotic days, mean (SD; range)</td>
<td>2.27 (3.07; 0.00, 12.00)</td>
<td>7.57 (4.34; 0.00, 16.00)</td>
<td>3.90 (2.22 to 6.64)*</td>
</tr>
<tr>
<td></td>
<td>NIHSS, mean (SD)</td>
<td>13.77 (8.27)</td>
<td>17.27 (9.78)</td>
<td>4.00 (0.12 to 7.88)§</td>
</tr>
<tr>
<td></td>
<td>Lowest % oxygen saturation, mean (SD)</td>
<td>93.87 (2.32)</td>
<td>85.15 (5.39)</td>
<td>-8.54 (–10.90 to –6.18)§</td>
</tr>
</tbody>
</table>

Final clinical outcome, n (%)

- Swallow improved: 20 (67) vs. 11 (36) (mean difference, 8.54; 0.16 (0.03 to 0.84)†; P = 0.031)
- Referred for PEG: 7 (23) vs. 12 (40) (mean difference, 8.54; 0.16 (0.03 to 0.84)†; P = 0.031)
- Treatment withdrawal: 3 (10) vs. 7 (23) (mean difference, 8.54; 0.16 (0.03 to 0.84)†; P = 0.031)

Clinical outcomes at 21 days after enrollment. Group-specific estimates are unadjusted. Between-group estimates are adjusted for age and baseline NIHSS score and are expressed with the placebo group as the reference group. CI indicates confidence interval; CRP, C-reactive protein; NGT, nasogastric tube; NIHSS, National Institutes for Health Stroke Scale; PEG, percutaneous endoscopic gastrostomy; and WBC, white blood cells.

*Rate ratio, †odds ratio, ‡fold change, and §mean difference (placebo–metoclopramide).

Abstract 11

Sex Differences in Short-Term Outcomes After Acute Ischemic Stroke

The Fukuoka Stroke Registry

Fumi Irie, MD; Masahiro Kamouchi, MD, PhD; Jun Hata, MD, PhD; Ryu Matsuo, MD, PhD; Yoshinobu Wakisaka, MD, PhD; Junya Kuroda, MD, PhD; Tetsuro Ago, MD, PhD; Takanari Kitazono, MD, PhD; on behalf of the FSR Investigators*

(Stroke. 2015;46:471-476.)

Key Words: brain infarction ■ prognosis ■ sex

급성뇌졸중 이후 단기 예후에서 성별간 차이
후쿠오카 뇌졸중 레지스트리

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배경과 목적
뇌졸중 이후 입상 결과에서 다양한 성별간 차이가 전 세계적으로 보고되고 있다. 이 연구의 목적은 성별이 급성뇌졸중 이후 나 türlü 재활적 예후와의 독립적인 위험인자를 밝히는 것이었다.

방법
1999년에서 2013년 사이 일본 후쿠오카 뇌졸중 레지스트리에 등록된 급성뇌졸중 환자의 데이터베이스를 사용하여, 이전에 독립적으로 지내다 처음으로 허혈뇌졸중이 발생한 환자로 중앙 발병 24시간 이내에 입원한 6236명을 대상으로 하였다. 초기 특성은 입원 시 평가하였다. 연구 결과는 심장학적 호전, 신경학적 악화, 나아가 기능적 예후(mRS 점수, 퇴원시 3–6점)를 포함하였다. 성별과 입상적 예후 사이의 관련성을 평가하기 위해 로지스틱 회귀분석을 실시하였다.

결과
이전에서 2398명(38.5%)이 여성이었다. 입원 시 심한 뇌졸중 (NIHSS 점수, ≥8)은 남성보다 여성에서 더 흔했다. 입원 중 신경학적 호전 또는 악화의 방향은 남녀 사이에 차이가 없었다. 연령, 뇌졸중 악화 및 증증도, 위험인자, 뇌졸중 이후 치료 등을 포 함하는 가능한 교환요인들을 보정한 이후, 여성 성별은 퇴원 시 나쁜 기능적 예후와 독립적으로 관련이 있었다(OR, 1.30; 95% CI, 1.08–1.57). 성별과 나쁜 예후 간의 관계는 연령에 따라 이질성 (heterogeneity)이 나타났다: 70세 이상의 환자에서는 남성보다 다 여성에서 나쁜 예후의 위험이 높았고, 70세 미만의 환자에서는 성별간의 명확한 차이가 나타나지 않았다.

결론
여성 성별은 급성뇌졸중 이후 퇴원 시 나쁜 기능적 예후의 위험과 관련이 있다.