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Evaluation of prokinetic agents used in the treatment of gastroparesis

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ABSTRACT

Background/Aim: Hospitalizations due to gastroparesis have increased in the last 20 years with limited advancements in pharmacologic therapy. Although therapy primarily consists of prokinetic agents, little is known about their effects on hospital outcomes. The aim of our study was to determine whether common prokinetic therapies (metoclopramide and erythromycin) improve outcomes in gastroparesis patients.

Methods: A retrospective review of adult patients admitted with a primary diagnosis of gastroparesis between 7 January 2011 and 7 January 2014 was conducted. Patients were divided into two groups based on whether they received prokinetic therapy (PRO) during hospitalization or not (NO). Groups were compared to determine length of stay (LOS), 30-day readmission rates, and risk factors affecting these outcomes.

Results: Of the 82 patients included in our study, 57 received prokinetic therapy. Mean length of stay (LOS) was 5.8 ± 4.2 days, with a significantly shorter LOS in the NO group (3.7 ± 1.9 vs. 6.7 ± 4.5; $p = 0.002$). Among patients studied, 30.5% were readmitted within 30 days from discharge with no significant reduction in the PRO group (35.1% PRO vs. 20% NO; $p = 0.23$). Patients with idiopathic gastroparesis had significantly longer LOS (6.9 ± 4.6 vs. 4.2 ± 2.8; $p = 0.003$). In the PRO group, those who received intravenous (IV) therapy had a significantly shorter LOS (4.9 ± 2.5 IV vs. 8.0 ± 5.3 oral; $p = 0.01$).

Conclusions: Treatment of gastroparesis patients with prokinetic agents did not shorten the LOS nor decrease 30-day readmission rates. In those receiving prokinetics, the IV route was associated with reduced LOS.

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Introduction

Gastroparesis is a gut motility disorder defined as delayed gastric emptying in the absence of mechanical obstruction. Cardinal symptoms include early satiety, postprandial fullness, nausea, vomiting, bloating, and upper abdominal pain [1]. While multiple conditions have been associated with gastroparesis, the majority of cases are idiopathic, diabetic, or postsurgical [1]. Regardless of etiology, there are limited medication treatment options available to patients with this disorder [2–4]. Hospitalizations with gastroparesis as the primary diagnosis have increased in the last 20 years with a dramatic increase occurring after the year 2000 [5]. In addition, some case series report an association between gastroparesis and increased rates of morbidity and mortality [6]. In view of these adverse outcomes, it is reasonable to hypothesize that gastroparesis and its complications may be associated with longer hospital stays and more frequent readmissions.

Primary treatment modalities for gastroparesis include restoration of fluids/electrolytes, nutritional support, and in diabetics, optimization of glycemic control [7]. Pharmacologic therapy consists of prokinetic and antiemetic agents. Metoclopramide, a dopamine receptor antagonist, serotonin 5-HT_4 receptor agonist, and weak inhibitor of 5-HT_3 receptors, is the most widely used prokinetic medication to treat patients with gastroparesis. Since gastric emptying of liquids is often preserved in gastroparesis, it has been hypothesized that the liquid formulation of metoclopramide is both safer and more effective [8]. Although widely used in gastroparesis, trial data for metoclopramide is limited to information from two to three decades ago [9–14]. Erythromycin, a macrolide antibiotic, is an alternative agent commonly used in gastroparesis due to its well-documented ability to promote gastric emptying through motilin receptor stimulation [15–17]. To this point, there are no head to head studies that address the effects of common pharmacologic regimens on length of stay or rates of readmission in patients with gastroparesis.

Given this lack of trial data and limited prokinetic agents available for use in the United States (metoclopramide and erythromycin), our aim was to conduct a retrospective review of patients diagnosed with gastroparesis to review medication therapies used and their effect on the primary endpoint of hospital length of stay. Secondary endpoints included rates of 30-day hospital readmission and adverse drug effects related to the therapies studied. Additionally, data points

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were analyzed to identify risk factors associated with increased length of hospital stay.

Methods

A retrospective review of patients admitted to Methodist LeBonheur Healthcare adult hospitals between 7 January 2011 and 7 January 2014 with a primary diagnosis of gastroparesis (ICD-9 diagnosis code of 536.3) was conducted. Due to the retrospective nature of the study, the diagnosis of gastroparesis was primarily based on chart diagnosis by physician alone. Patients who were ≥18 years old were included. We excluded patients who received ≥1 but <3 doses of a study prokinetic (metoclopramide, erythromycin) or received other medications known to have prokinetic effects (azithromycin, cisapride, domperidone, lubiprostone). Since this study was conducted in the United States, domperidone use was excluded. Also excluded were those who had postsurgical gastroparesis, patients who had undergone surgical procedures to correct gastroparesis, and those being treated with gastric electrical stimulation.

Patients were divided into two groups based on whether they received a prokinetic therapy during hospitalization or not. Group I (PRO) includes patients who received ≥3 doses of metoclopramide, erythromycin, or both medications during admission. Group II (NO) includes patients who did not receive any prokinetic therapy during hospitalization. Patient charts were then reviewed for pertinent demographics, length of stay, laboratory results, gastric emptying studies, therapies received, and incidences of adverse effects.

Statistical analysis

Categorical data were evaluated with the Fisher's exact test, while the *t*-test was used to evaluate continuous data. The primary outcome of hospital length of stay was calculated as a mean ± standard deviation. This data point was compared between groups as continuous data using the Student's *t*-test. Statistical significance was defined a priori as a $p < 0.05$. All statistical analyses were performed with the SPSS statistical program, version 20 (Chicago, IL).

Results

One hundred four patients with a primary diagnosis of gastroparesis were screened, with 82 patients meeting inclusion criteria. Of these, 57 patients received prokinetic therapy (PRO group), while 25 were categorized into the no prokinetic treatment group (NO group). Baseline characteristics (reported in Table 1) were similar between groups. In the PRO group, 53 patients received metoclopramide monotherapy, one patient received erythromycin monotherapy, and three received combination therapy. These groups were compared for predefined risk factors that may have impacted LOS and readmission rates (Table 2). While there were no statistically significant differences, there was a higher rate of home opioid use in the PRO group (26%) compared to the NO group (16%; $p = 0.4$).

Table 1. Baseline characteristics.

Characteristics	PRO ($n = 57$)	NO ($n = 25$)	p value
Age – yr. (mean ± SD)	49 ± 16	51 ± 16	0.60
Male gender, no. (%)	13 (22.8)	7 (28)	0.78
Race, no. (%)			
African–American	35 (61.4)	16 (64)	1.00
White	21 (36.2)	9 (36)	1.00
Asian	1 (1.9)	0	–
Weight – kg (mean ± SD)	84 ± 28	105 ± 89	0.11
Positive GE Scan, no. (%)	28 (49.1)	8 (32)	0.23
Diabetic, no. (%)	22 (38.6)	12 (48)	0.47

GE: gastric emptying.

Table 2. Predefined risk factors.

Risk factor, *n* (%)	PRO ($n = 57$)	NO ($n = 25$)	p value
Any BG >200 mg/dl	21 (36.8)	9 (36)	1.00
Opioid as home medication	15 (26)	4 (16)	0.40
Received during admission:			
Opioid	45 (79)	18 (72)	0.53
Tricyclic antidepressant	6 (10.5)	0	0.17
No antianxiety medication	34 (59.6)	15 (60)	1.00

BG = blood glucose.

Overall mean LOS was 5.8 ± 4.2 days, with a significantly shorter LOS in the NO group (3.7 ± 1.9 vs. 6.7 ± 4.5; $p = 0.002$). Among all patients studied, 30.5% were readmitted to one of our system hospitals within thirty days from discharge with no reduction of this rate seen in the PRO group (35.1% PRO vs. 20% NO; $p = 0.23$) despite 76% of PRO patients being discharged on prokinetic therapy. The 30-day readmission diagnosis was gastroparesis related in 100% of the NO group compared to 70% of the PRO group ($p = 0.29$). As shown in Table 3, the overall rate of adverse effects was 34%, with no statistically significant increase in the PRO group.

Analyses conducted to identify factors associated with poorer hospital outcomes revealed that patients who had documented delayed gastric emptying had a significantly longer LOS than those who did not (8 ± 4.9 vs. 4.8 ± 0; $p < 0.001$). Increased LOS (Table 4) was also identified in those who never received an antiemetic medication (13.1 ± 8.4 vs. 5.5 ± 3.7; $p = 0.001$) and those who had apparent idiopathic gastroparesis (6.9 ± 4.6 vs. 4.2 ± 2.8; $p = 0.003$). Within the PRO group, patients who received intravenous (IV) therapy had a significantly shorter LOS (4.9 ± 2.5 days vs. 8.0 ± 5.3 days; $p = 0.01$). While not reaching statistical significance, patients who received daily metoclopramide doses of ≥40 mg/day versus <40 mg/day had a shorter LOS (5.74 ± 3.8 vs. 7.35 ± 5.1; $p = 0.19$).

Discussion

Gastroparesis is a gut disorder with multiple complications but limited pharmacologic treatment options [1]. Very few studies have been published comparing prokinetic treatments and those that exist are several decades old with limitations related to study size and/or design [9–14]. Additionally, to our knowledge, none have described treatment impact on hospital length of stay or rates of readmission – two very important metrics for both disease control and the current healthcare financial model.

Table 3. Hospital outcomes.

Length of stay, days (mean ± SD)	PRO ($n = 57$)		NO ($n = 25$)	p value
Overall LOS	6.7 ± 4.5		3.7 ± 1.9	0.002
IV vs. PO (n)[a]	4.9 ± 2.5 (23)	8.0 ± 5.3 (31)	N/A	0.01
Metoclopramide daily dose[b]			N/A	
40 mg vs. 15 mg (n)	5.5 ± 3.7 (23)	8.5 ± 5.9 (7)	N/A	0.12
40 mg vs. 20 mg (n)	5.5 ± 3.7 (23)	7.0 ± 4.9 (23)	N/A	0.23
≥40 mg vs. <40 mg (n)	5.7 ± 3.8 (25)	7.4 ± 5.1 (31)	N/A	0.18
30-day readmission, n (%)	20 (35.1)		5 (20)	0.23
Safety – adverse events, n (%)				
Overall incidence	20 (35)		8 (32)	1.0
Extrapyramidal symptoms	3 (5.3)		0	0.55
QTc >450 milliseconds	17 (29.8)		8 (32)	1.0

[a]Three patients receiving both oral and intravenous treatment were excluded from this analysis.
[b]Four patients who also received erythromycin were excluded from this analysis.

Table 4. Risk factor impact on length of stay.

Length of stay, days (mean ± SD)	Patients with risk factor	Patients with no risk factor	p value
Predefined			
Opioid as home medication	$n = 19$	$n = 63$	0.20
	6.8 ± 5.1	5.4 ± 3.8	
Received during admission:			
Opioid	$n = 63$	$n = 19$	0.65
	5.6 ± 4.2	6.1 ± 4	
Tricyclic antidepressant	$n = 6$	$n = 76$	0.39
	7.1 ± 6.2	5.6 ± 3.9	
Antianxiety medication	$n = 33$	$n = 49$	0.24
	6.4 ± 4.2	5.3 ± 4.1	
Any BG >200 mg/dl	$n = 30$	$n = 52$	0.35
	5.2 ± 4.2	6.1 ± 4.1	
Identified post-hoc			
Idiopathic gastroparesis	$n = 34$	$n = 48$	0.003
	4.2 ± 2.8	6.9 ± 4.6	
Antiemetic medication	$n = 79$	$n = 3$	0.001
	5.5 ± 3.7	13.1 ± 8.4	

In our study, guideline recommended prokinetic treatments for gastroparesis did not improve hospital outcomes of LOS nor rates of 30-day readmission. Overall rates of 30-day readmission in our study were similar if not higher than seen in other chronic conditions associated with frequent readmissions, such as heart failure [18] and chronic obstructive pulmonary disease [19]. Interestingly, patients in our study who did not receive prokinetic treatment had a shorter mean LOS and lower rates of 30-day readmission, which could be explained by the severity of disease. We concluded that milder disease patients may not receive pharmacologic therapy for their gastroparesis; thereby, skewing the results for LOS and readmission rates. Controlling for this factor in *post hoc* analysis was difficult due to poor documentation of disease severity scores, such as the gastroparesis cardinal symptom index (GCSI), in the inpatient setting.

To identify factors that improved care in those requiring prokinetics for disease control, we compared within the PRO group various aspects of treatment to identify factors associated with improved hospital outcomes. Due to the limited number of patients who received erythromycin, treatment analyses were limited primarily to metoclopramide. Among patients receiving metoclopramide, those who received treatment via the intravenous route had a shorter LOS than those who received it via the oral route. According to treatment guidelines, first-line prokinetic therapy is metoclopramide given orally in a liquid dosage form to facilitate absorption [1]. The clinical benefit of the liquid formulation, however, is only theoretical and is based on the pathophysiology of gastroparesis but has not been validated in studies. Using this same logic, it could be theorized that intravenous treatment would be of even greater benefit due to its complete bioavailability even in the setting of decompensated gastroparesis. Our study supports this theoretical benefit as evidenced by a reduction in length of hospital stay in those receiving intravenous dosing.

Treatment guidelines recommend use of metoclopramide at the lowest effective dose for each patient beginning with 5 mg three times daily up to a maximum recommended dose of 40 mg per day [1]. While not reaching statistical significance, our study demonstrated a trend toward a dose-related treatment effect on LOS with patients receiving greater doses having shorter LOS. Based on these results, there may be clinical benefit in using doses closer to the recommended daily maximum in patients who present to the hospital with poorly controlled gastroparesis. While this treatment approach might raise concern for increasing rates of adverse drug effects, our study did not demonstrate this occurrence. The overall percentage of patients experiencing an adverse drug effect in our study was 34%, a larger than expected percentage that was primarily driven by our strict definition for a prolonged QT interval. Rates of adverse events were similar between groups, regardless of the dose used. Three patients reportedly experienced extrapyramidal symptoms due to metoclopramide, with two of them receiving 20 mg daily and the third receiving 40 mg daily.

An important aspect in the management of gastroparesis is avoiding or removing modifiable risk factors for disease exacerbation [1]. As part of our study, we sought to identify modifiable as well as non-modifiable risk factors associated with worse hospital outcomes. The only modifiable factor associated with worse outcomes in our study was whether or not patients received antiemetic therapy. Those who were not treated with an antiemetic agent had a statistically significant increase in LOS, however the overall number of patients analyzed in this group was extremely small.

Our study does have limitations that should be addressed. First, it is retrospective in nature and relied on ICD-9 coding to identify the primary diagnosis used for our inclusion criteria. It also relied on chart review for the collection of relevant patient data such as medical history and risk factors. The low number of patients in certain subgroups made it difficult to assess some outcomes. Very few patients received

erythromycin and only a small number of patients received the guideline recommended liquid formulation of metoclopramide when oral administration was used. At the time of this study, our institution did not have a diet for gastroparesis so we were unable to assess how this management strategy might have affected outcomes. Also, in describing 30-day readmission rates, we were only able to capture readmissions to our system hospitals.

Despite these limitations, our study offers useful observations for gastroparesis and its treatment, particularly when considering the number of patients included compared to existing literature. Prior studies evaluating prokinetic treatment of gastroparesis have primarily described its effects on gastric emptying and symptom improvement [5,7,10]. To our knowledge, this study is the first to describe prokinetic treatment effects on LOS and 30-day readmission. Additionally, our study describes the overall rate of 30-day readmission in patients hospitalized for the treatment of gastroparesis – an epidemiological metric not previously seen in the gastroparesis literature. Finally, our study demonstrates treatment strategies that yield both statistical and clinical benefit warranting evaluation in future prospective trials.

Conclusions

In conclusion, this study did not demonstrate the benefit of prokinetic therapy on either LOS or 30-day readmission rates in patients with gastroparesis. Among those treated with a prokinetic agent, rates of adverse drug events were not significantly increased and the IV route was associated with a reduction in LOS. Risk factors associated with poorer hospital outcomes were identified. Each of these findings offers insight for gastroparesis therapy and could serve as the basis for future studies evaluating pharmacologic based treatment of this disorder.

Transparency

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Declaration of financial/other interests

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