

Efficacy and Safety of Ondansetron versus Metoclopramide Treatment in Infants with Gastroesophageal Reflux Disease: A Comparative Study of Short Trial

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ABSTRACT

OBJECTIVE: To compare the efficacy and safety of ondansetron versus Metoclopramide in infants with gastroesophageal reflux disease (GERD).

METHODOLOGY: This single-centre, randomized controlled trial was conducted at the Pediatric Medicine outpatient department, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, from July to December 2024. Infants aged 1–12 months with GERD refractory to conservative management were randomized (1:1) to receive oral Metoclopramide or ondansetron for one week. Eligible infants were enrolled using a simple random sampling technique. Diagnosis was based on clinical history and exclusion of hypertrophic pyloric stenosis by ultrasound. Treatment response ($\geq 70\%$ reduction in vomiting episodes and weight preservation/gain) and adverse events were assessed at follow-up. Data were analyzed using SPSS v26.0, with $p < 0.05$ considered statistically significant.

RESULTS: Of 284 enrolled infants, 154 (54.2%) were male. The median age was 7.00 (IQR 4.00–10.00) months. Rural residence was noted in 200 (70.4%) infants, and exclusive breastfeeding in 144 (50.7%). A total of 271 infants (95.4%) completed follow-up (Metoclopramide: $n=136$, ondansetron: $n=135$). Treatment response occurred in 225 (83.0%) infants, with no significant difference between metoclopramide (79.4%) and ondansetron (86.7%) groups ($p=0.112$). Adverse events were relatively similar between groups for diarrhea (20.6% vs 22.2%, $p=0.743$) and lethargy (10.3% vs 11.9%, $p=0.683$). Warm flushes (5.9%) and constipation (2.2%) were observed only with ondansetron.

CONCLUSION: In infants with GERD, ondansetron appears to offer acceptable efficacy, reinforcing its position as a preferred agent where resources permit. Metoclopramide remains an appropriate alternative, particularly in settings where access or cost are significant considerations.

KEYWORDS: Diarrhea, GERD, infant, ondansetron, metaclopramide.

INTRODUCTION

Gastroesophageal reflux (GER) is a common physiological phenomenon in infancy, affecting up to 40–67% of healthy infants in the first three to four months of life^{1,2}. While most cases are benign and resolve spontaneously, a subset of infants develop gastroesophageal reflux disease (GERD), characterized by persistent regurgitation associated with complications such as poor weight gain, feeding refusal, esophagitis, recurrent wheezing, and other respiratory symptoms³. Epidemiological studies estimate that GERD affects approximately 10–15% of infants, necessitating medical evaluation and intervention⁴. The clinical burden of GERD is significant, contributing to frequent outpatient visits, parental anxiety, and substantial healthcare costs^{5v}. First-line management of GERD in infants emphasizes non-pharmacological strategies, including modification of feeding techniques, thickened feeds, hypoallergenic formula trials, and optimal positioning⁶. Despite these

measures, many infants continue to experience troublesome symptoms, and pharmacologic therapy becomes necessary⁷. Available treatment options, however, are limited by safety concerns and variable efficacy. H₂-receptor antagonists and proton pump inhibitors, though commonly prescribed, are not uniformly effective in infants and may be associated with adverse events such as increased risk of infections^{6,8}. Prokinetic agents, once a cornerstone of therapy, are now used sparingly. Domperidone has largely been abandoned in pediatric practice following regulatory warnings of life-threatening cardiac arrhythmias and sudden cardiac death⁹. Metoclopramide, though still used, carries the risk of neurological side effects such as extrapyramidal symptoms and tardive dyskinesia, limiting its long-term use¹⁰. These limitations underscore the need for safer, effective alternatives for infant GERD.

In recent years, interest has emerged in ondansetron, a selective serotonin 5-HT₃ receptor antagonist primarily indicated for the prevention of chemotherapy- and surgery-induced nausea and vomiting¹¹. Ondansetron has demonstrated a favorable safety profile in pediatric populations, particularly with respect to cardiac and neurological adverse effects compared to traditional prokinetics¹². Its mechanism of action, involving modulation of vagal afferents and

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doi: 10.22442/jlumhs.2025.01364

Received: 14-07-2025

Revised: 02-09-2025

Accepted: 04-09-2025

Published Online: 12-09-2025



gastric motility, suggests potential benefit in GERD management. However, clinical evidence for its use in infants with GERD remains sparse. Given the unmet need for safer and more effective pharmacologic options, and in the absence of prior direct comparisons, this study was planned to evaluate and compare the efficacy and safety of ondansetron versus Metoclopramide in infants with GERD.

METHODOLOGY

This single-centre, parallel-group, randomized controlled trial was conducted at the outpatient department of Pediatric Medicine, Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan, from July to December 2024. Ethical approval was obtained from the Institutional Review Board before study commencement (letter number: PM.U-I/008/79/A.I.T Hosp, D.G.K, dated: 8-3-2024). This clinical trial was registered as NCT06898268 (<https://clinicaltrials.gov>). Written informed consent was secured from the parents or guardians of all participating infants. Confidentiality and voluntary participation were ensured throughout the study process. The inclusion criteria were infants of either gender, aged between 1 and 12 months, who presented with symptoms suggestive of GERD refractory to standard conservative management, including dietary modifications and positional therapy. The diagnosis of GERD was based on clinical history, such as repeated episodes of regurgitation or vomiting containing milk, occurring immediately or within 30 minutes of feeding. All infants underwent ultrasonographic evaluation to exclude hypertrophic pyloric stenosis (HPS) before enrollment. Infants were excluded if they had congenital heart disease, a history of any significant prior illness with gastrointestinal symptoms, concurrent febrile illness, abdominal distension, vital instability at the time of presentation, evidence of neurological impairment (such as severe developmental delay or microcephaly), or ultrasonographic findings consistent with HPS. Conservative management was defined as dietary modifications (smaller, more frequent feeds, thickened feeds, and trials of hypoallergenic formula where indicated), as well as positional therapy (keeping the infant upright for at least 20–30 minutes after feeding). Refractory GERD was defined as persistence of ≥ 3 vomiting or regurgitation episodes per day with associated distress, feeding refusal, or poor weight gain despite at least two weeks of standard conservative management. A sample size of 284 infants (142 per group) was determined based on expected differences in treatment efficacy between the two interventions of 10%, considering a two-sided significance level of 0.05 and a power of 80%. Eligible infants were enrolled using a simple random sampling technique.

Baseline demographic data, including age, gender, and mode of feeding (exclusive breastfeeding, formula, or mixed feeding), were recorded at

enrollment. Each infant underwent a thorough clinical assessment. Participants were randomized into either the Metoclopramide or the ondansetron group using a computer-generated randomization sequence. Participants allocated to the Metoclopramide Group received oral Metoclopramide at a dose of 0.1–0.15 mg/kg per dose, administered every 12 hours, half an hour before feeds, for a duration of one week. Those randomized to Group B received oral ondansetron, matched for dose and frequency (0.1–0.15 mg/kg per dose, every 12 hours, 30 minutes before feeding, for one week). Caregivers were instructed on the administration and adherence to the recommended dosage regimens. Caregivers were also provided with written and verbal instructions regarding medication administration, recognizing side effects, and the importance of compliance and follow-up. Participants returned for in-person evaluation seven days after initiation of therapy. At follow-up, response to treatment was defined a priori as a $\geq 70\%$ reduction in vomiting episodes compared to baseline, accompanied by preservation or increase in body weight. Adverse events like diarrhea, constipation, warm flushes, lethargy or somnolence, dark urine, and episodes of inconsolable crying without an apparent cause were documented. Infants unable to visit at the scheduled follow-up after 1 week were excluded from the final analysis.

Data analysis was performed using IBM-SPSS Statistics version 26.0. The Shapiro-Wilk test was applied to assess the normality of continuous variables. Categorical variables (gender, feeding mode, treatment response, adverse events) were reported as frequencies and percentages, while continuous variables were expressed as mean and standard deviation. Between-group comparisons for categorical outcomes were performed using the chi-square or Fisher's exact test, as appropriate. For continuous variables, Student's t-test or Mann-Whitney U test was used based on data distribution. Statistical significance was defined as a two-tailed p-value < 0.05 .

Trial Registration:

NCT06898268 (<https://clinicaltrials.gov>)

RESULTS

In a total of 284 infants, there were 154 (54.2%) who were male, and 130 (45.8%) who were female. The median age was 7.00 (4.00–10.00) months, while the mean weight was 7.01 ± 1.03 kg. 200 (70.4%) infants resided in rural areas. Exclusive breastfeeding was documented in 144 (50.7%) infants. No significant difference was found with respect to gender distribution among infants of study groups ($p=0.475$). Age was statistically similar among infants of the metoclopramide and ondansetron groups ($p=0.474$). Gender distribution was statistically identical among participants of both study groups ($p=0.603$). Comparison of baseline characteristics among study groups is shown in **Table I**.

Table I: Baseline characteristics of infants (n=284)

Characteristics	Metaclopramide group (n=142)	Ondansetron group (n=142)	P-value
Gender	Male	80 (56.3%)	0.475
	Female	62 (43.7%)	
Age (months)	7.00 (4.00-10.00)	7.00 (4.00-10.00)	0.474
Weight (kg)	6.91±1.00	7.11±1.05	0.100
Residence	Urban	44 (31.0%)	0.603
	Rural	98 (69.0%)	
Feeding mode	Exclusive breastfeeding	69 (48.6%)	0.726
	Formula	48 (33.8%)	
	Mixed	25 (17.6%)	

Of 284 infants, 271 (95.4%) turned up for the final evaluation and were included in the final analysis (136 in the metoclopramide group, and 135 in the ondansetron group). Thirteen infants (4.6%) were lost to follow-up, thus excluded from outcome evaluation. **Figure 1** shows the CONSORT flow diagram.

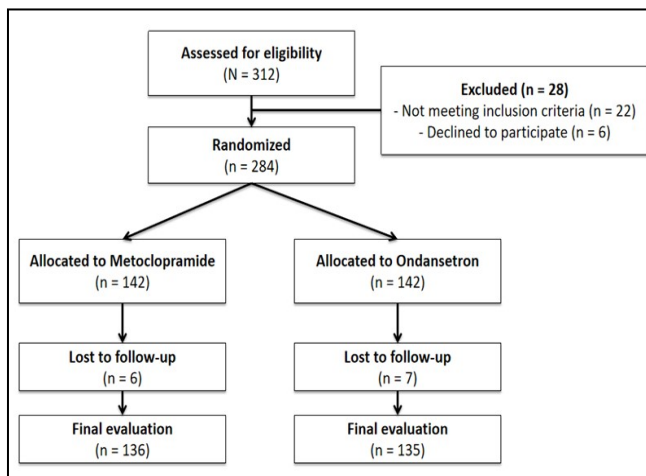


Figure 1: CONSORT flow diagram

Overall, treatment response was reported in 225 (83.0%) infants. Treatment response was observed in 108 of 136 infants (79.4%) in the metoclopramide group, versus 117 of 135 infants (86.7%) in the ondansetron group, and the difference in response rates was not statistically significant (p=0.112). Diarrhea was reported in 28 (20.6%) infants in the metoclopramide group, and 30 (22.2%) in the ondansetron group (p=0.743). Lethargy or somnolence was noted in 14 (10.3%) infants in the metaclopramide group, and 16 (11.9%) infants in the ondansetron group (p=0.683). Warm flushes were observed only in the ondansetron group (5.9% vs. 0%, p=0.004). Constipation was reported in 3 (2.2%) infants in the ondansetron group and none in the metoclopramide group (p=0.080). No cases of dark urine or unexplained inconsolable crying were reported in either group.

Table II shows a comparison of effectiveness and safety among infants studied in both groups.

Table II: Comparison of effectiveness and safety in infants between study groups (n=271)

Outcomes	Meta-clopramide group (n=136)	Ondansetron group (n=135)	P-value	
Treatment response	Yes	108 (79.4%)	0.112	
	No	28 (20.6%)		
Side effects	Diarrhea	28 (20.6%)	0.743	
	Lethargy or somnolence	14 (10.3%)	0.683	
	Warm flushes	-	8 (5.9%)	0.004
	Constipation	-	3 (2.2%)	0.080

DISCUSSION

This study reported an overall treatment response of 83.0% across the cohort, with a numerically higher response rate observed in the ondansetron group compared to Metoclopramide (86.7% vs 79.4%). However, the difference did not reach statistical significance (p = 0.112). In the study by Ahmad M et al.¹³ ondansetron demonstrated a 92.5% efficacy in the cessation of vomiting at 24 hours in children with acute gastroenteritis, outperforming both domperidone (77.5%, p = 0.03) and Metoclopramide. The slightly higher response in Ahmad M et al.¹³ may be attributable to differences in the patient population, as the study included children with acute gastroenteritis across a wider age range. In contrast, the present trial focused exclusively on infants with clinically diagnosed GERD. Parallel observations emerged in the network meta-analysis by Barot KS et al.¹⁴ which synthesized data from 19 randomized controlled trials to assess the antiemetic efficacy in pediatric acute gastroenteritis. This synthesis revealed that ondansetron was significantly more effective than placebo in achieving cessation of vomiting, and was superior to both domperidone and Metoclopramide. In this context, the results of the present trial reinforce ondansetron's standing as a preferred agent for symptomatic management of vomiting in pediatric patients, and expand its evidence base to include infants with GERD. This population has not been

extensively studied in previous trials. The results of the present study are also in agreement with those reported by Khan A et al.¹⁵ who compared ondansetron and Metoclopramide in children with acute gastroenteritis. The efficacy of ondansetron was 96.4%, which was significantly higher than that of Metoclopramide (82.1%). This difference, while numerically larger than the gap observed in the present study, may be related to the older mean age and a potentially higher baseline likelihood of spontaneous resolution in the Khan A et al.¹⁵ cohort. The present trial's focus on infants with GERD addresses an essential gap in the literature, where most published studies concentrate on older children and on vomiting due to gastroenteritis rather than reflux. A double-blind trial by Al-Ansari K 2011¹⁶ among children with persistent vomiting secondary to gastroenteritis found that both intravenous ondansetron and Metoclopramide were similarly effective, with cessation of vomiting observed in 81% and 72% of cases, respectively ($p=0.14$). The response rates in the present trial closely mirror those reported by Al-Ansari K 2011¹⁶ further validating the results. The lack of a statistically significant difference in efficacy between the two agents in both studies may reflect the high baseline response rate to antiemetics in pediatric vomiting, as well as potential limitations related to sample size or study power. A systematic review by Sumie M et al.¹⁷ focusing on the use of ondansetron versus Metoclopramide for postoperative nausea and vomiting (PONV) in pediatric tonsillectomy patients demonstrated a significantly lower risk of PONV with ondansetron and a shortened length of hospital stay. The review also found no difference in readmission rates or extrapyramidal side effects, although these outcomes were infrequently reported. Regional data from Iran in a randomized trial of 116 neonates with resistant GERD, treated with omeprazole plus Metoclopramide, showed a higher response rate (93.7%, $p=0.028$) than ranitidine plus Metoclopramide (75.4%)¹⁸. No adverse effects occurred, indicating that Metoclopramide is more effective when combined with a PPI than with an H2-blocker.

In this study, no serious adverse events or treatment discontinuations were recorded, and adverse effects were generally mild and transient. Diarrhea was the most frequently reported adverse event in both groups, occurring in 20.6% of metoclopramide-treated infants and 22.2% of those receiving ondansetron, with no statistically significant difference. Barot KS et al.¹⁴ and Ahmad M et al.¹³ documented that adverse events related to common pharmacological approaches in the given context were minimal and comparable. The higher rate of diarrhea reported in the present study may be a function of the young age of participants or differences in diagnostic criteria and event reporting. Warm flushes, reported in 5.9% of ondansetron-treated infants and in none of the metoclopramide group, reached statistical significance

($p=0.004$). While this finding warrants attention, it was not associated with clinical deterioration or treatment discontinuation, and has not been commonly reported as a significant issue in previous studies. Constipation was infrequent, affecting 2.2% of ondansetron recipients and none in the metoclopramide group ($p=0.080$). These findings align with reports from Sumie M et al.¹⁷ and Afacan MA 2019¹⁹ who found that adverse events related to both study agents were rare or absent, and not associated with significant clinical consequences. The absence of extrapyramidal symptoms or severe neurological adverse events, particularly in the metoclopramide group, provides reassurance regarding the safety of both interventions in infants when used at recommended doses.

The systematic review by Hibbs AM 2006²⁰ highlighted substantial heterogeneity in dosing, study populations, and outcome measures across included studies when analyzing the role of Metoclopramide for the treatment of infantile GERD, with the majority demonstrating some degree of patient improvement, but limited high-quality evidence supporting safety and efficacy¹⁹. The present trial directly addresses this gap, providing high-quality, prospectively collected comparative data and supporting the continued use of Metoclopramide as a therapeutic option in the management of infantile GERD, albeit with a signal toward greater efficacy with ondansetron^{21,22}.

Pharmacokinetic modelling studies have suggested that metoclopramide doses in the range used in the present trial result in drug exposures within the suggested efficacy range for infants^{23,24}. The pharmacokinetic evidence provides a mechanistic basis for the observed clinical outcomes and supports the appropriateness of the dosing regimen employed in this trial. While ondansetron emerges as a preferred agent based on pooled efficacy data and safety, considerations of cost, drug availability, and local practice patterns remain relevant, particularly in resource-limited settings.^{25,26} Metoclopramide continues to play a role as a less expensive alternative with a favorable safety profile when used appropriately. The present findings thus offer practical guidance for clinicians in diverse settings, supporting a rational approach to antiemetic selection in infants with GERD.

The implications of these findings for clinical practice are substantial. The high efficacy and safety profile of ondansetron supports its use as a preferred agent for managing refractory vomiting in infants with GERD, where available and affordable. The similar safety profile and only slightly lower efficacy of Metoclopramide mean that it remains a viable option, especially where resource constraints preclude routine use of ondansetron. Despite these strengths, several limitations merit consideration. A broader, multicenter design would enhance the external validity of the results and capture potential variations in efficacy or adverse event rates across different demographic and clinical settings. Exclusion of infants unable to attend

the final evaluation introduces a potential for attrition bias. However, the proportion lost to follow-up was relatively low and unlikely to have materially influenced the observed results. The outcome assessment relied on caregiver-reporting, which, while clinically relevant and pragmatic, may be subject to recall or measurement bias. Employing objective, validated symptom scoring systems and regular, standardized weight measurements in future trials could further strengthen the evidence base. The study could have included a placebo group, reflecting both ethical and pragmatic considerations, but this would have limited conclusions about the absolute efficacy of either agent relative to natural disease resolution. Future research could address these gaps by utilizing blinded, placebo-controlled, multicenter designs with extended follow-up periods and standardized outcome measures.

CONCLUSION

Both ondansetron and Metoclopramide are effective and well-tolerated pharmacologic options for the management of refractory GERD symptoms in infants. Ondansetron appears to offer acceptable efficacy, reinforcing its position as a preferred agent where resources permit. Metoclopramide remains an appropriate alternative, particularly in settings where access or cost are significant considerations. The absence of severe adverse events and the low incidence of problematic side effects provide reassurance regarding the appropriateness of both drugs in carefully selected infant populations.

Acknowledgments: The authors would like to thank Muhammad Aamir Latif (RESnTEC) for his assistance in trial registration of this research.

Ethical permission: D.G Khan Medical College, Dera Ghazi Khan, Pakistan, ERC letter No. PM.U-I/008/79/A.I.T Hosp, D.G.K.

Conflict of Interest: No conflicts of interest, as stated by the authors.

Financial Disclosure / Grant Approval: No funding agency was involved in this research.

Data Sharing Statement: The corresponding author can provide the data on a reasonable request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Jabeen I: Data collection, drafting, responsible for data's integrity, approved for final publication.

Akbar A: Conception, data analysis, critical revisions, approved for publication.

Ahmed S: Conception, design, proofreading, critical revisions, approved for publication.

Ilyas S: Data collection, drafting, responsible for data's integrity, approved for final publication.

Asmatulah: Data collection, drafting, responsible for data's integrity, approved for final publication.

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