

Sublingual ondansetron for treatment of acute gastroenteritis in children in the children's emergency

Dear Editor,

Acute gastroenteritis (GE) is a leading cause of death globally in children aged below 5 years and the third most common indication for hospital admission in some countries.^{1,2} Currently, norovirus is the most common cause of GE in children in developed countries.³ Rehydration, either orally or intravenously, is the mainstay of treatment to prevent multisystemic complications of dehydration.⁴ In recent decades, there has been increased interest in the role of antiemetics (such as ondansetron) in acute GE to reduce the need for intravenous rehydration, hospital admissions, emergency department reattendances, and healthcare expenditure.^{5,6}

Ondansetron use in GE has been found to be superior to placebo and other antiemetics in reducing further vomiting, and the need for intravenous hydration and hospitalisation.^{7,8} Meta-analyses have shown that ondansetron use for GE in the children's emergency (CE) significantly reduces hospitalisation compared to placebo (relative risk [RR] 0.53, 95% confidence interval [CI] 0.29–0.97 versus OR 2.93, 95% CI 1.69–6.18).^{8,9} Given the ease of administration and increasing evidence of its safety and efficacy, paediatric centres have incorporated the use of ondansetron into their practice guidelines.^{10,11} However, there is a paucity of evidence regarding factors associated with its success or failure for acute GE in children. Our centre's practice in the CE, National University Hospital, Singapore has been to give a trial of fluids after ondansetron administration, and review the children 30 minutes later to determine ondansetron success or failure. This creates a patient dwell time of 1–2 hours from the point of CE consultation. Thus, identifying factors that can predict success or failure with ondansetron can help clinicians distinguish between patients at high risk of failure with a likely need for monitoring in CE, versus patients who can be discharged early postondansetron.

We report the results of our retrospective cohort study involving paediatric patients (6 months to 18 years of age) who presented with vomiting and received ondansetron at the CE between 1 January and 31 December 2018. This retrospective study was approved by the National Healthcare Group Domain Specific Review Board (Reference number: 2018/01394).

In our practice, patients are given a trial of fluids 30 minutes after ondansetron administration, and then reviewed 30 minutes later to ensure there is no further vomiting before discharge. Inclusion criteria for this study included a clinical diagnosis of acute GE and prescription of sublingual ondansetron in the CE consequently. Patients with alternative diagnoses for their symptoms or who required intravenous therapy were excluded. Patients were identified through pharmacy records. Data extraction from electronic medical records included demographics, vital signs, weight, day of illness, number of vomiting episodes, associated symptoms such as diarrhoea or fever, hydration status, dose of ondansetron given, and outcome post-ondansetron. Outcomes were defined as: (1) early success: successful trial of fluids in CE after sublingual ondansetron; (2) early failure: failed trial of fluids in CE after sublingual ondansetron; (3) total success: successful trial of fluids, not requiring admission and no reattendance within 3 days of initial consult; and (4) total failure: failure of trial of fluids at initial consult, need for admission and any reattendance within 3 days of initial consult. Statistical analysis was performed using SPSS Statistics software version 26.0 (IBM Corp, Armonk, US).

We identified 3,146 patients who fulfilled the inclusion criteria. Of these, we excluded the following: patients with no ongoing vomiting ($n=117$), and uncertain outcome post-ondansetron (e.g. abscondment or early discharge prior to clinical assessment) ($n=50$). Data of the remaining 2,979 patients were analysed (Fig. 1).

The mean age of patients diagnosed with GE who received sublingual ondansetron was 4.79 ± 4.03 years and over 50% (1,608/2,979) were males. Average duration of illness upon CE presentation was 1.66 ± 1.19 days (range 1–11 days). Regarding hydration status, 89.8% were a euvolemic, 9% were mildly dehydrated, 1.1% were moderately dehydrated while 0.03% were severely dehydrated (Supplementary Table S1).

Early success was observed in 95.8% (2,854/2,979) of patients. Of these, 2.2% (63/2,854) were admitted nevertheless due to (1) parental request ($n=32$); (2) patients requiring intravenous rehydration as a result of clinical dehydration ($n=13$); (3) persistent symptoms such as dizziness, nausea or lethargy ($n=8$); (4)

investigation of abdominal pain ($n=3$); and (5) abnormal vital signs and repeated healthcare visits ($n=7$) (Fig. 1).

A further 7.1% (203/2,854) reattended at CE within 3 days of initial presentation for persistent gastrointestinal symptoms ($n=156$) and non-gastrointestinal symptoms ($n=47$); 53.7% (109/203) of these reattendances required admission. Reattendances with persistent gastrointestinal symptoms were more likely to require admission compared with those who reattended for other complaints (60.3% vs 31.9%, $P<0.001$). Total success rate (i.e. successful trial of fluids after ondansetron

dose, not admitted and no reattendance within 3 days for any reason) was 86.9% (2,588/2,979) (Fig. 1).

Early failure was observed in 4.2% (125/2,979) of patients. Over 95% (119/125) of these patients were subsequently admitted; 6 were not admitted due to parental preference. Rate of total failure was 13.1% (391/2,979), comprising early failures, eventual admissions despite initial success with ondansetron, and reattendances despite initial success (Fig. 1).

Clinical features associated with early failure versus early success with ondansetron in paediatric GE included older age (6.5 vs 4.7 years, $P=0.008$),

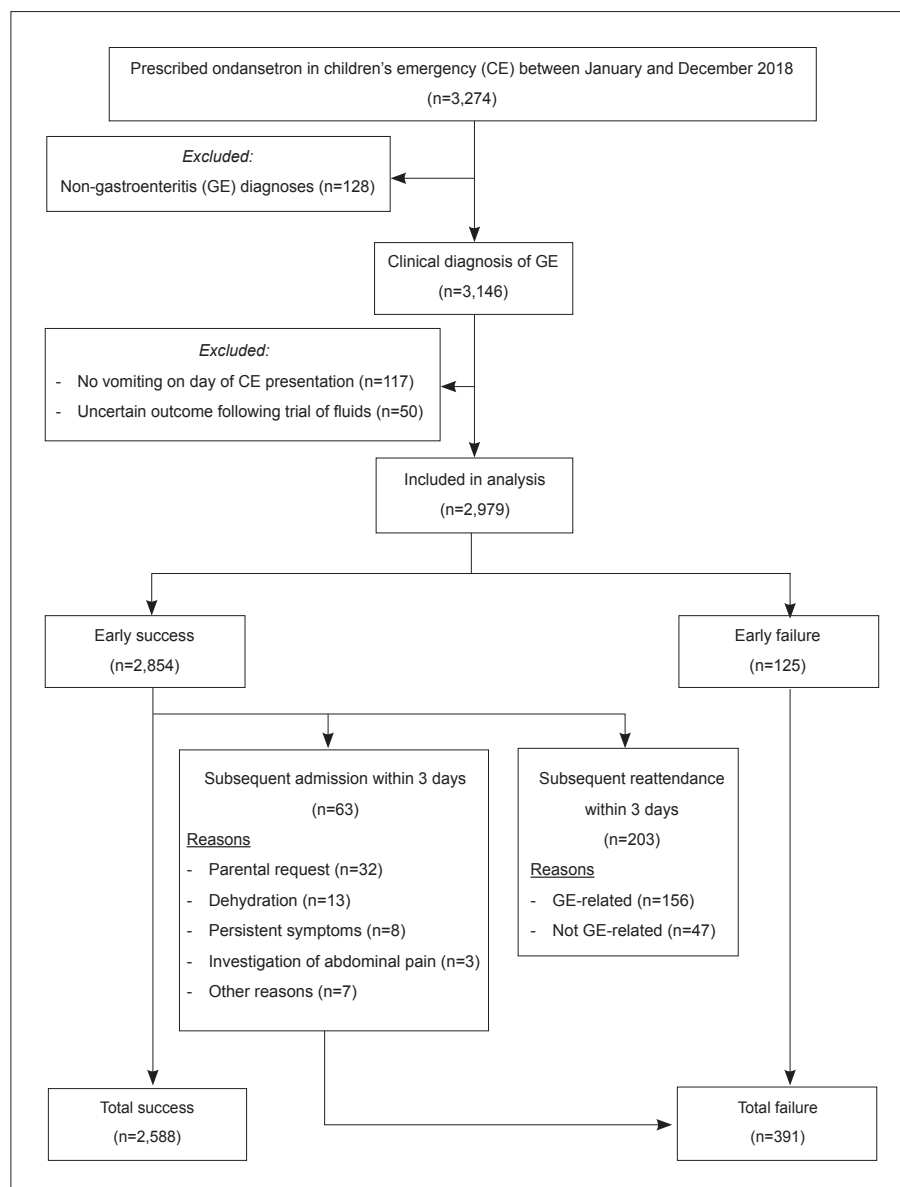


Fig. 1. Study flowchart.

CE: children's emergency; GE: gastroenteritis

higher number (≥ 6) of vomiting episodes prior to CE presentation (46.4% vs 35.9%, $P=0.017$) and dehydration (30.4% vs 9.3%, $P<0.001$) (Supplementary Table S2). Subgroup analysis revealed that children ≥ 5 years old were more likely to be dehydrated ($P<0.001$) and present with a higher number of vomiting episodes ($P<0.05$) compared with children under 5. Dehydration was the only factor significantly associated with total failure versus total success (22.8% vs 8.3%, $P<0.001$) (Supplementary Table S3).

Our study demonstrated high efficacy with sublingual ondansetron for acute GE in CE. These findings agree with previous studies on the efficacy of ondansetron in viral gastroenteritis and support the continued use of this drug for such clinical indication.^{12,13} Closer attention should be paid to older children, children who present with higher number of vomiting episodes, and children with evidence of dehydration, as they are more likely to experience early failure with ondansetron. We included admissions and reattendances both related and unrelated to GE or ondansetron failure under the “total failure” outcome as this accurately reflects real-life clinical setting. Most reattendances were unrelated to gastrointestinal symptoms, and also less likely to truly require admission. Physicians may therefore consider pre-empting parents on the expected course of viral infections and provide anticipatory guidance in order to reduce unnecessary CE visits.

The strength of our study is its large sample size. Limitations include its retrospective nature, missing data, possible non-standardised assessment of patients by physicians, probable recall bias from parental report of symptoms, and possible underestimation of the total failure rate (as patients may have sought medical attention elsewhere after discharge from our CE). Apart from the need for prospective, follow-up studies to confirm our findings, studies on the utility and safety of sublingual ondansetron in primary care settings are warranted.

Acknowledgement

We thank Ms Sheena Nishanti D/O Ramasamy for her assistance in editing, formatting and, submitting the manuscript for publication.

REFERENCES

1. World Health Organization. Child mortality (under 5 years), 28 January 2022. <https://www.who.int/news-room/fact-sheets/detail/levels-and-trends-in-child-under-5-mortality-in-2020>. Accessed 26 March 2022.
2. Lo Vecchio A, Dias JA, Berkley JA, et al. Comparison of Recommendations in Clinical Practice Guidelines for Acute Gastroenteritis in Children. *J Pediatr Gastroenterol Nutr* 2016; 63:226-35.
3. Payne DC, Vinjé J, Szilagyi PG, et al. Norovirus and medically attended gastroenteritis in U.S. children. *N Engl J Med* 2013; 368:1121-30.
4. Guarino A, Bruzzese E, Lo Vecchio A. Oral Rehydration Solution—An Essential Therapy for Childhood Gastroenteritis. *JAMA Pediatr* 2018;172:991.
5. Freedman SB, Steiner MJ, Chan KJ. Oral ondansetron administration in emergency departments to children with gastroenteritis: an economic analysis. *PLOS Med* 2010;7:e1000350.
6. Hervás D, Armero C, Carrión T, et al. Clinical and economic impact of oral ondansetron for vomiting in a pediatric emergency department. *Pediatr Emerg Care* 2012;28:1166-8.
7. Danewa AS, Shah D, Batra P, et al. Oral Ondansetron in Management of Dehydrating Diarrhea with Vomiting in Children Aged 3 Months to 5 Years: A Randomized Controlled Trial. *J Pediatr* 2016;169:105-9.e3.
8. Niño-Serna LF, Acosta-Reyes J, Veroniki AA, et al. Antiemetics in Children With Acute Gastroenteritis: A Meta-analysis. *Pediatrics* 2020;145:e20193260.
9. Tomasiak E, Ziolkowska E, Kołodziej M, et al. Systematic review with meta-analysis: ondansetron for vomiting in children with acute gastroenteritis. *Aliment Pharmacol Ther* 2016;44:438-46.
10. Children's Health of Orange County. Outpatient Acute Gastroenteritis Guideline, 20 January 2016. <https://www.choc.org/wp/wp-content/uploads/careguidelines/OutpatientAcuteGastroenteritisGuidelines.pdf>. Accessed 18 March 2022.
11. The Royal Children's Hospital Melbourne. Clinical Practice Guidelines: Gastroenteritis, December 2020. https://www.rch.org.au/clinicalguide/guideline_index/Gastroenteritis. Accessed 18 March 2022.
12. King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 2003;52(RR-16):1-16.
13. Colletti JE, Brown KM, Sharieff GQ, et al. The management of children with gastroenteritis and dehydration in the emergency department. *J Emerg Med* 2010;38:686-98.

Olivia Leow¹ *MMED (Singapore),*

Davina Neeta Paul² *MBBS (Singapore),*

Anh Phuong Tran¹ *BSc,*

Yang Chern Lim¹ *MMED (Singapore),*

Velda Xinying Han¹ *MMED (Singapore),*

Andrea Yeo¹ *MMED (Singapore)*

¹ Department of Paediatrics, Khoo Teck Puat-National University Children's Medical Institute, Singapore

² Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Correspondence: Dr Velda Xinying Han, Department of Paediatrics, Khoo Teck Puat-National University Children's Medical Institute, 1E Kent Ridge Road, NUHS Tower Block Level 12, Singapore 119228. Email: velda_han@nuhs.edu.sg