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Oral ondansetron for paediatric gastroenteritis in primary care: a randomised controlled trial

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ABSTRACT

Background: Acute gastroenteritis affects almost all children younger than 5 years. Due to vomiting the standard oral rehydration therapy (ORT) treatment is less effective. In secondary care, ondansetron was found to be effective in reducing vomiting.

Aim: To determine the effectiveness of adding oral ondansetron to care-as-usual on vomiting in children with acute gastroenteritis attending out-of-hours primary care.

Design and setting: A pragmatic randomised controlled trial with a follow-up of 7 days, at three out-of-hours primary care centres.

Method: Inclusion criteria: 1) age 6 months to 6 years, 2) acute gastroenteritis diagnosed by a general practitioner, 3) at least four reported episodes of vomiting in the 24 hours before presentation, 4) at least one reported episode of vomiting in the 4 hours before presentation, and 5) written informed consent from both parents. The control group received care-as-usual (ORT). The intervention group received care-as-usual plus one dose of oral ondansetron (0.1 mg/kg).

Results: In total, 194 children were included for randomisation. One dose of oral ondansetron decreased the proportion of children who continued vomiting within 4 hours from 42.9% to 19.5%, with an odds ratio of 0.37 (95% CI = 0.20–0.72, NNT 4). Ondansetron also decreased the number of vomiting episodes within 4 hours, incidence rate ratio of 0.51 (95% CI, 0.29-0.88), and improved overall parental satisfaction with treatment (p = 0.027).

Conclusions: Ondansetron decreased vomiting and increased parental satisfaction in children with acute gastroenteritis. We were not able to show an increased ORT intake or decrease in referral rate.

Keywords (6): Acute gastroenteritis, oral ondansetron, primary care, out-of-hours, children, vomiting

How this fits in

Ondansetron was found to be effective in reducing vomiting in secondary care, but this effect has never been evaluated in primary care. Based on the findings of this study, ondansetron use is effective in reducing vomiting from 42.9% to 19.5%, seems safe and is positively evaluated by parents. Therefore, ondansetron could be considered by general practitioners as an additional treatment in the management of dehydration due to acute gastroenteritis, when the child predominantly vomits. Future research should disentangle the key factors leading to hospital referrals and consider ways to administer ORT more effectively in primary care or at home.

INTRODUCTION

Acute gastroenteritis (AGE) is common in young children, and although it is typically self-limiting, severe dehydration is an important complication (1). About 5% of all general practitioner (GP) consultations with children in the Netherlands are for AGE (2). Among those seen in primary care, 8.1% are referred to specialist care and 8000 are admitted to the hospital each year (2,3). However, it is thought that many of these referrals and admissions can be avoided (4).

International guidelines recommend care-as-usual (CAU) with oral rehydration therapy (ORT) to prevent and treat dehydration in children (5). It has been shown that prescribing ORT with education can reduce hospital admission by up to 45% (4,6–8), yet it is still underused in primary care. Indeed, only 4% of all children with AGE received ORT by their GP (9,10). A suggested reason for this underuse is that 70% of these children present with vomiting as the predominant symptom (9). Pediatrics national guidelines mention persistent vomiting as a predictor of ORT failure in dehydrated children (11). As such, most GPs are less likely to prescribe ORT when the child predominantly presents with vomiting (12).

Ondansetron has been reported to be safe and effective for stopping vomiting, increasing ORT success, and reducing hospitalization rates among children presenting with AGE in secondary care (13). However, the practical value of ondansetron for treating children with AGE in primary care is unknown. We therefore aimed to conduct a pragmatic randomised controlled trial to investigate the effect of ondansetron added to CAU, compared to CAU alone, on vomiting in children aged 6 months to 6 years consulting out-of-hours primary care (OOH-PC) with AGE.

METHODS

Study design

We enrolled participants from December 2015 until January 2018 at three OOH-PC in the north of the Netherlands, located in Groningen, Zwolle, and Assen. A detailed description of the study design, recruitment strategy, outcomes, and discussion of the informed consent procedure are described elsewhere (14). This study started with a pilot (NL4700) from December 2015 until October 2016 but because of the low inclusion rate the primary outcome was changed from 'referrals' to 'vomiting'. In agreement with the Medical Ethics Review Committee of the University Medical Centre of Groningen, included children from the pilot were also included in the new trial (NL5830) and the randomised controlled trial was approved.

Inclusion and exclusion criteria

Children considered to be at increased risk of dehydration (15) were included if they met the following inclusion criteria: 1) age 6 months to 6 years; 2) diagnosis of AGE confirmed by a GP at the OOH-PC; 3) at least four reported episodes of vomiting 24 hours prior to presentation at the OOH-PC; and 4) at least one reported episode of vomiting 4 hours prior to presentation.

We then excluded any children who met the following criteria: 1) used, or prescribed, anti-emetics in the previous 6 hours; 2) known renal failure or hypoalbuminemia; 3) known diabetes mellitus or inflammatory bowel disease; 4) a history of abdominal surgery that could explain the current symptoms (according to the GP); 5) known sensitivity to 5-HT3 receptor antagonists; 6) known prolonged QT interval, or current use of QT prolonging medication; and 7) previous enrolment in the study.

Randomisation and blinding

Randomisation occurred after we obtained written informed consent from the consulting

parent plus verbal informed consent of the second parent (in most cases, he or she was at home). After gaining consent, we randomly allocated children to one of the two intervention groups in a 1:1 ratio. An online randomisation tool was used to generate the allocation sequence in direct response to participant inclusion by the research assistant; concealment was not an issue because allocation was only generated after randomisation. The allocation sequence was stratified by age (6–24 or >24 months) and severity of dehydration ("at risk" for no alarm symptom or "dehydrated" for ≥1 alarm symptom). Comparison between groups were adjusted for these stratification factors. We additionally excluded those children for whom no extended written informed consent of the second parent was received. Exclusion was performed after randomisation because of protocol violation as set by the Medical Ethics Review Committee.

Participants, parents, GPs, and research assistants were not blinded to the allocated treatment. Ondansetron has already been proven effective in reducing vomiting in blinded randomised controlled trials (16,17). In this pragmatic randomised controlled trial we specifically aimed to investigate the potential effect of implementing ondansetron in routine primary care. Blinding participants would in this case result in outcomes not translatable to daily practice. The statistician performing the analyses was blinded to the treatment allocation by an independent researcher. The primary outcome was not known by parents and GPs.

Interventions

Control group: Care-as-usual

Care-as-usual (CAU) comprised instructions to buy oral rehydration solution, including how to use it, as described in the acute diarrhoea guideline of the Dutch College of General Practitioners (15): 10 mL/kg compensation when at risk of dehydration (i.e. all children) and 15 mL/kg for 4 hours if a GP assessed dehydrated. The research assistant provided instructions with a patient folder containing the same information, discussed alarm symptoms,

and advised to contact the GP if there was no improvement or if symptoms worsened (15).

The intervention: ondansetron added to care-as-usual

Children allocated to the intervention group received the CAU described above plus a single weight-based dose of oral ondansetron syrup (0.1 mg/kg), in accordance with the Dutch Pediatrics Formulary (18). If the child vomited within 15 minutes, the same dose was repeated once, but a third dose was not given.

Outcomes

Parents completed diaries for 7 days. For the first 4 hours after presentation, they reported hourly, thereafter, they reported daily until 7 days after presentation. If parents did not return the diary after multiple request, we collected information about the primary outcome by telephone.

Primary outcome

The primary outcome was the proportion of children who continued vomiting in the first 4 hours after randomisation. We chose this evaluation point because the circulating concentration of ondansetron is expected to reach 50% of its maximum serum level at 3 hours after oral dosing, meaning that direct effects on vomiting are unlikely beyond 4 hours (18). In addition, national guidelines recommend GPs to evaluate the effect of treatment on symptoms and assess the indications for referral in children with AGE by 4 hours after initial presentation (8,11,15).

Secondary outcomes

The following outcomes were assessed up to 4 hours after randomisation: the number of vomiting episodes per case, the ORT intake (millilitres per participant), and the proportion of children who experienced ≥1 adverse events related to ondansetron. The following outcomes were assessed up to 7 days after randomisation: the proportion of children referred to

specialist care, and the proportion of children admitted to hospital. Finally, we assessed parental satisfaction with ondansetron therapy using a five-point Likert scale.

Statistical methods

Sample size

Based on a systematic review, we estimated that 85% of children in the CAU group and 64% of children in the intervention group would continue vomiting within 4 hours (13). We calculated that 100 children per group were needed to achieve an alpha of 0.05 and a power of 0.90. To compensate for an expected loss to follow-up of 10%, we aimed to include 220 children (19,20). For the intention-to-treat (ITT) analysis, we were able to include 88 and 87 children in the intervention- and control group respectively. Therewith the power remained above the 80% (sample size n=166).

Handling of missing data

We explored by the use of logistic regression if baseline characteristics were related to missing values on our outcomes. For all single outcomes, further inspection of frequencies and distribution of values, gave no indication that the missing values were related to the true values themselves (i.e. values were distributed as theoretically expected). In addition, Little's MCAR test was not significant (p-value chi-square: 0.76). Thus, we assumed the missing data to be missing at random (21). See Supplementary Table 1 for an overview of the baseline characteristics of complete cases versus participants with missing values. All available participant data were entered as predictors in multiple imputation: baseline characteristics, outcomes, and any available variables potentially related to outcomes. After analyses on 20 separate multiple imputed datasets, we pooled the results. In line with the STROBE and CONSORT guidelines, we also performed all analyses on cases with complete data only.

Main analyses

Data were analysed on both an ITT and a per protocol (PP) basis. In addition, analyses were performed on both multiple imputed data and complete cases. We assumed that the pooled estimates of ITT analyses on our multiple imputed data would be most reliable, and as such, we considered these our main analyses. All analyses were performed using IBM SPSS Version 25 (IBM Corp., Armonk, NY, USA).

The ITT population consisted of all patients randomly allocated to one of the two treatment groups, regardless whether they received, or adhered to, the allocated intervention. The only excluded participants were those who violated the inclusion- or met the exclusion criteria (i.e. no informed consent of the second parent or retraction of informed consent).

The PP population consisted of the ITT population, but also excluded participants if they either did not receive treatment, deviated from the protocol, or withdrew from the study.

Primary and secondary outcome analyses

In all analyses, the treatment group was the independent predictor. The primary outcome "continued vomiting" was evaluated by logistic regression, and because all included participants vomited at baseline, we did not adjust our analyses for baseline status. The secondary outcome "number of vomiting episodes" was analysed with a log-linear negative binomial model. The secondary outcomes "summed millilitres of ORT intake" and "parental satisfaction" were analysed with a Mann–Whitney *U* test. The secondary outcomes "referred," "admitted," and "adverse events" were evaluated with logistic regression.

Sensitivity analyses

We performed sensitivity analyses on our pre-specified primary and secondary outcome "number of vomiting episodes," excluding the first hour (i.e., from 2–4 hours only).

RESULTS

Study participants

We screened 1061 participants aged 6 months to 6 years old who presented with vomiting at one of the three participating primary care OOH-PC. In total, 867 children were excluded with no diagnosis of AGE (n=227) and not eligible because we intended to included children at increased risk of dehydration (n=395) as the most common reasons. Hereof, we included and randomised 194 children, 97 to the CAU and intervention group (Figure 1). Unfortunately, 16 cases were excluded because parents did not return their written informed consent forms, despite initially giving their oral informed consent, and 3 parents withdrew informed consent after randomisation. Thus, data for 175 participants were available for ITT analysis. Another 17 children did not receive the allocated intervention and 6 were lost to follow-up, resulting in 152 participants available for the PP analyses (Figure 1).

Included participants had a median age of 1.5 years (Range: 6 months to 6 years), 50% were female, the median duration of vomiting before presentation was 2 days (Range 0.8–9.0 days), and 71% had diarrhoea. There were no essential differences in baseline characteristics between the CAU and the intervention groups in either the ITT (Table 1) or the PP (Supplementary Table 2) populations. The most common risk factor was fever (24.9%) and the most common alarm symptoms was no urine output for 24 hours (14.3%).

There was a wide range of missing data for the variables used in the composite measures (12%–49%). In total, 154 participants provided all data needed for the primary outcome measure (88% of the 175 included children) (Table 2).

Outcomes

The effect of ondansetron on continued vomiting and vomiting episodes

The pooled estimates of ITT analyses on the multiple imputed data were considered as the main analyses. Ondansetron decreased the proportion of children who continued vomiting

within the first 4 hours after randomisation from 42.9% to 19.5% (Table 2). This corresponded with a relative risk of 0.60 (95% CI = 0.45–0.81) and number needed to treat of 4 (OR = 0.37, 95% CI = 0.20–0.72). In the intervention group, children had fewer vomiting episodes within the 4 hours after randomisation when compared with the CAU group, where the incidence rate ratio was 0.51 (95% CI = 0.29–0.88). We found similar estimates when repeating the analysis in the PP population (Supplementary Table 3).

The effect of ondansetron on ORT intake, referrals, and hospital admissions

Intake of ORT, number of referrals, and number of hospital admissions did not significantly differ between treatment groups. In both treatment groups, the median ORT intake within 4 hours was 10 mL, referral occurred for 19% of all children, and most referred children were admitted to hospital (74% of all referred children, or 14% of all included children) (Table 2).

Associated adverse events and parental satisfaction with ondansetron

Ondansetron did not increase the occurrence of adverse events. The median (interquartile range) parental satisfaction with treatment after one week was significantly higher in the intervention group than in the CAU group, with values of 4.0 (4.0–5.0) and 4.0 (3.0–4.0), respectively (p = 0.027) (Table 2).

Sensitivity analyses

In the sensitivity analysis, the effect of ondansetron on continued vomiting during the first 4 hours after randomisation remained significant (OR = 0.44, 95% CI = 0.23–0.87), but the number of vomiting episodes did not differ between treatment groups (incidence rate ratio = 0.62, 95% CI = 0.34–1.13) .

DISCUSSION

Summary

One dose of ondansetron given in an OOH-PC setting decreased the proportion of participants with AGE who had persistent vomiting by 50%. Overall, ORT intake was low (10 mL/4h) and referral rates were high (19% in comparison to a mean referral rate of 8.1% (3)). Ondansetron use did not appear to increase ORT intake, nor did it lead to fewer hospital referrals or admissions. Nevertheless, parents were more satisfied with the addition of ondansetron compared with ORT alone.

Strengths and limitations

We are aware of no other studies investigating the practical effectiveness of ondansetron on vomiting and other important treatment goals in children with AGE, when parents consult an OOH-PC. Other strengths of this study are that nearly 600 GPs collaborated over a more than two-year period, and that we were able to gather data about the reasons for exclusion. From these data it becomes clear that we selected the subgroup of children who at presentation frequently vomited, as was intended. In addition, the use of an hourly diary for the first 4 hours also provided us with detailed and reliable data on our primary outcome.

Limitations of the study were that there was a wide range of missing values measures (range: 12%–49%). Although, we found no association between missing values and either treatment, the findings based on these secondary outcome measures should be interpreted with caution. It could also be seen as a limitation that we did not blind participants, i.e. parents and GPs for the intervention. Although it is disputable whether this would have been desirable in a pragmatic trial, we do think it did not influence the primary outcome measurement. First, because we wanted to investigate the potential effect of implementing ondansetron in routine primary care and second, because assessors of outcome were blinded.

Comparison with existing literature

The finding that oral ondansetron reduces the incidence of vomiting and the proportion of

vomiting episodes within 4 hours after presentation at an OOH-PC is consistent with results of others (13, 24). We were able to add that this effect of ondansetron on vomiting persisted over a 4-hour period. In addition, our results indicate that a 0.1 mg/kg dose of ondansetron in primary care is at least comparable effective in inducing vomiting cessation as a higher dose given in the emergency department.

Despite the prescription of ORT for all included children by research assistants, the reported ORT intake was low in both treatment groups. Interestingly, studies from emergency department settings indicate that ORT can have a success of 100% when prepared and administered by qualified and trained nurses directly after giving an ondansetron dose (23). It would also be interesting to study alternatives to ORT that children can better tolerate or accept at home, such as diluted apple juice (24). However, for the CAU we followed the guideline of the Dutch College of General Practitioners (25), which do not include the use of apple juice.

There could be several reasons for the high referral rate among children with AGE and frequent vomiting. First, a plausible explanation for the high referral rate may be that it reflects a lack of success with ORT at home. The median intake of oral rehydration solution, 10 mL in 4 hours, was considered ineffective for children at any age. Finding ways to improve ORT success at home seems to be key to rectifying this issue. Second, because vomiting cessation did not lower referral rates, the decision to refer a child with AGE may have been influenced by considerations other than risk factors for dehydration and hydration status. Such factors may include how parents interpret and communicate symptoms of dehydration, the related health care seeking behaviour of parents, and how exactly GPs follow up on their paediatric patients after discharge from the OOH-PC (26).

Treatment groups had comparable rates of adverse events, consistent with the findings of a systematic review and meta-analysis (17). The review showed that the number and type of

adverse events was comparable between oral ondansetron and placebo groups, with no serious adverse events. Although the use of ondansetron in primary care seems safe, further monitoring and reporting for potential side-effects is still indicated when it is prescribed.

Implications for research and/or practice

Ondansetron use is effective and seems safe, while being positively evaluated by parents, when used to stop vomiting among children presenting in primary care with AGE and vomiting. Therefore, we advocate that ondansetron be considered an add-on treatment for use by GPs when managing dehydration due to AGE and frequent vomiting in primary care. However, our findings also show that ondansetron alone will not substantially affect ORT intake, nor will it reduce the high referral rate to specialized care. Future research should disentangle the key factors leading to hospital referral for children with AGE. Finally, research should also consider ways to administer ORT more effectively in primary care or at home, such as direct administration by nurses, better parental education, and the use of alternatives for ORT.

Table of abbreviations

AGE	Acute gastroenteritis
CAU	Care-as-usual
GP	General Practitioner
ITT	Intention-to-treat
OOH-PC	Out-of-hours primary care
ORT	Oral rehydration therapy
PP	Per protocol

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Author's contribution: IB and AW are the primary investigators and are responsible for analysis and drafting the manuscript. GH supervised the study, helped to design the study, and contributed to developing the research protocol. HR, FF, HV, and BK helped to design the study, and critically reviewed the manuscript. MB supervised the study, helped to design the study, and contributed to developing the research protocols.

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Conflict of Interest Statement: All authors have completed the Unified Competing Interest form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Trial registration: Dutch Trial Register identifier: Trial NL5830 (https://www.trialregister.nl/trial/5830).

Data Sharing Statement*:* De-identified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis

plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to g.a.holtman@umcg.nl.

Ethical approval

This study was conducted according the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subject Act and other guidelines, regulations, and acts. The trial was approved by the Medical Ethical Committee of the University Medical Centre of Groningen and was registered in the Dutch Trial Register (NL5830).

Transparency declaration

The manuscript's guarantors affirm that this is an honest, accurate and transparent account of the study being reported: that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

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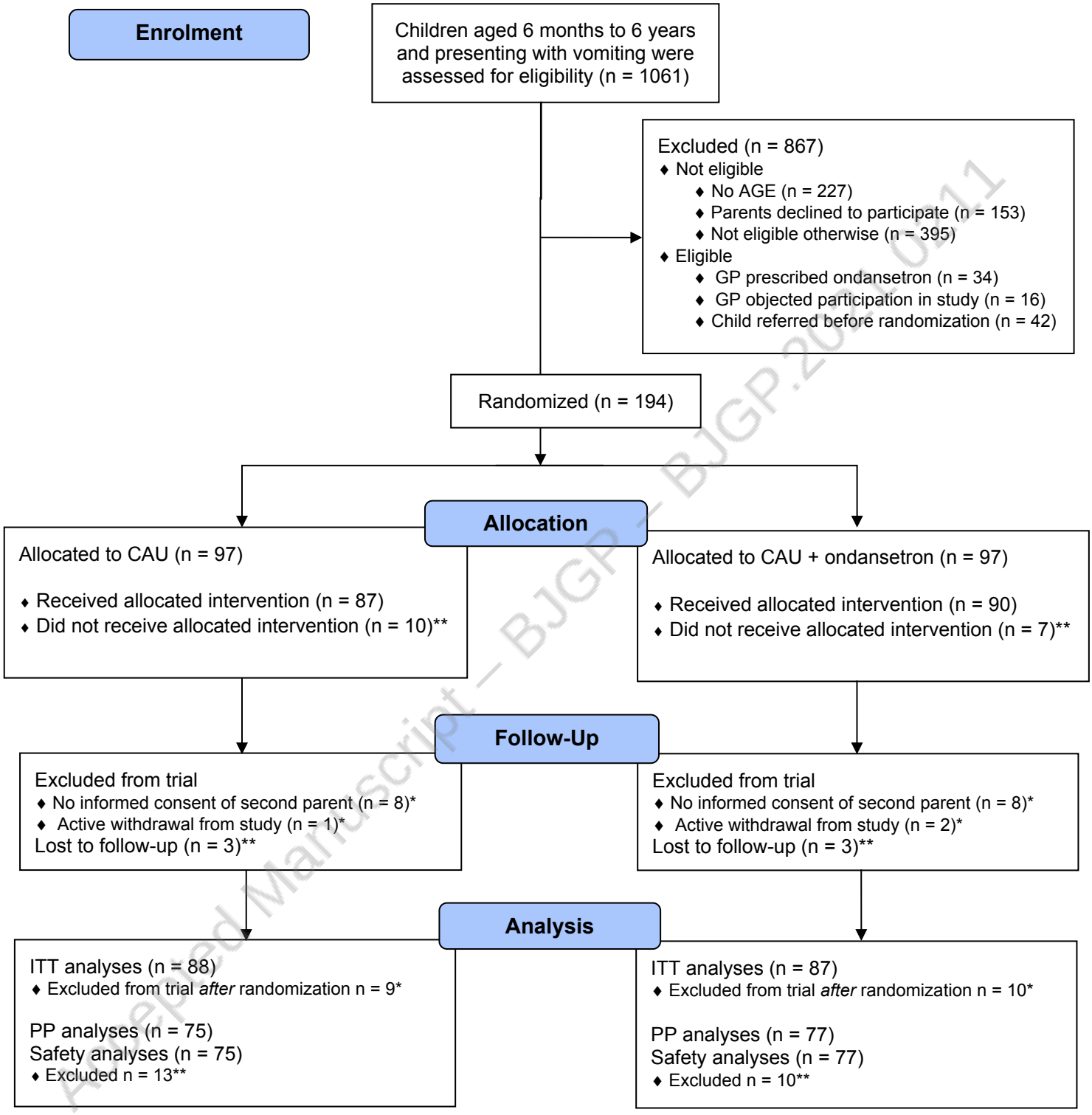
Figure 1. Study flow diagram



*Excluded from trial because of no informed consent of second parent or active withdrawal from study (retracted informed consent).
**Excluded from PP and safety analyses because participants did not receive the allocated intervention or data were lost to follow-up.
Abbreviations: CAU = care as usual; GP = general practitioner; ITT = intention to treat; PP = per protocol

Table 1. Baseline characteristics of the intention-to-treat population (N = 175)

Baseline characteristics	Valid N	**Participants** (N = 175)	Valid N	**CAU** (N = 88)	Valid N	**Intervention** (N = 87)
Age in years, Median (IQR)	175	1.5 (0.9–2.1)	88	1.5 (0.9–2.0)	87	1.5 (0.9–2.2)
Females, N (%)	175	88 (50.3)	88	50 (56.8)	87	38 (43.7)
Weight in kg, Median (IQR)	169	11.0 (9.5–14.0)	86	11.0 (9.4–14.0)	83	12.0 (9.5–14.3)
Duration of vomiting prior to presentation in days, Median (IQR)	174	2.0 (1.0–3.0)	87	1.2 (1.0–2.0)	87	2.0 (1.0–3.0)
Frequency of vomiting past 24 hours, Median (IQR)	171	5.0 (4.0–10.0)	86	5.0 (4.0–10.0)	85	6.0 (4.0–10.0)
Diarrhoea present, N (%)	174	124 (71.3)	87	66 (75.9)	87	58 (66.7)
Duration of diarrhoea prior to presentation in days*, Median (IQR)	124	2.0 (1.0–3.0)	66	1.0 (0.4– 2.0)	58	1.0 (0.0–3.0)
Frequency of diarrhoea in past 24 hours*, Median (IQR)	123	3.0 (2.0–5.0)	66	2.0 (1.0–5.0)	57	1.5 (0.0–4.0)
How dehydrated is the child? (0-100%), Median (IQR)	170	20.0 (10.0–40.0)	85	20.0 (6.0–40.0)	85	20.0 (10.0–40.0)
Use of concomitant medication, N (%)	175	65 (37.1)	88	31 (35.2)	87	34 (39.1)
Additional risk factors of dehydration**						
1, N (%)	175	63 (36.0)	88	33 (37.5)	87	30 (34.5)
≥2, N (%)	175	18 (10.3)	88	10 (11.3)	87	8 (9.2)
Alarm symptoms of severe dehydration***						
1, N (%)	175	32 (18.3)	88	15 (17.0)	87	17 (19.5)
≥2, N (%)	175	2 (1.1)	88	1 (1.1)	87	1 (1.1)

CAU = care as usual. IQR = interquartile range.
*Numbers only presented for those participants with diarrhoea.
**Risk factors assessed at baseline were: ≥ 6 watery stools or diarrhoea, fever, reduced intake.
***Alarm symptoms assessed at baseline were: confused or decreased consciousness, bradycardia, weak peripheral heartbeat pulsations, capillary refill >4 s, extremities cold/marbled, and no urine output for 24 hours.

Table 2. The effect of ondansetron on primary and secondary outcomes of the intention to treat population

The effect of ondansetron on primary and secondary outcomes	Valid N	Participants (N = 175)	Valid N	CAU (N = 88)	Valid N	Intervention (N = 87)	Valid N	Imputed cases	Non-imputed cases
Continued vomiting hour 1-4, N (%)	154	48 (31.2)	77	33 (42.9)	77	15 (19.5)	154	**0.37 [0.20, 0.72]#**	**0.32 [0.16, 0.66]#**
Vomiting episodes hour 1–4, median (Range)*	137	0.0 (0.0–6.0)	67	0.0 (0.0–6.0)	70	0.0 (0.0–5.0)	137	**0.51 [0.29, 0.88]##**	0.46 [0.21, 1.03]##
Intake ORT in ml, median (IQR)	88	10.0 (0.0–100.0)	46	0.0 (0.0–72.0)	42	35.0 (0.0–180.0)	88	0.522###	0.093###
Referrals, N (%)	144	28 (19.4)	73	14 (19.2)	71	14 (19.7)	144	1.19 [0.60, 2.36]#	1.04 [0.45, 2.36]#
Hospital admissions, N (%)	132	19 (14.4)	73	10 (13.7)	59	9 (15.3)	132	1.80 [0.91, 3.55]#	1.13 [0.43, 3.00]#
Adverse events, N (%)**	96	30 (31.3)	48	19 (39.6)	48	11 (22.9)	96	0.63 [0.34, 1.17]#	0.45 [0.19, 1.10]#
Serious adverse events, N (%)***	91	6 (6.6)	46	4 (8.7)	45	2 (4.4)	91	0.83 [0.45, 1.54]#	0.49 [0.09, 2.81]#
Parental satisfaction, median (IQR)	107	4.0 (3.0–4.0)	53	4.0 (3.0–4.0)	54	4.0 (4.0–5.0)	107	**0.027###**	**0.013###**

CAU = Care as usual. IQR = interquartile range. ORT = Oral rehydration therapy. **Bold** = significant difference.
*Complete range provided instead of IQR because data are heavily skewed (IQR = 0–0).
**Adverse events: erythema, hic-ups, headache.
***Serious adverse events: spasms/convulsions, breathing problems.
#Odds ratio [95% confidence interval]
##Incident rate ratio [95% confidence interval]
###P-value of the Mann–Whitney *U* test