

Treatment of giardiasis in children: Randomized trial of rectal metronidazole versus oral tinidazole

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1 **Abstract**

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3 *Objectives:* We investigated the efficacy, safety and acceptance of rectally administered
4 metronidazole for the treatment of giardiasis in children.

5 *Patients and Methods:* This study (ClinicalTrials.gov Identifier: NCT02942485) was an open-labeled
6 randomized comparison of a 3-day-course of rectal metronidazole and single-dose oral tinidazole in
7 children with giardiasis. Clinical cure was defined as the resolution of symptoms by day 10 post-
8 treatment. Microbiological eradication was assessed with stool enzyme immunoassay for
9 *G.duodenalis* antigen on day 7-10 post-treatment.

10 *Results:* The study was terminated due to the extremely slow enrollment. We describe the outcome
11 for six patients treated with rectal metronidazole and one patient treated with oral tinidazole. All
12 symptomatic patients (4/4) were clinically cured with rectal metronidazole. Microbiological
13 eradication was successful after the first treatment course in all tested patients (6/6), of whom five
14 were treated with rectal metronidazole and one with oral tinidazole. Side effects were reported in one
15 patient and were restricted to a single episode of loose stool after the third dose of rectal
16 metronidazole. The majority of caregivers (4/6) considered the administration of rectal metronidazole
17 relatively easy.

18 *Conclusions:* We provide a proof of principle for the efficacy of rectally administered metronidazole
19 in the treatment of giardiasis.

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21 **Key words:** Giardia duodenalis, nitroimidazole, pediatric

22 **Conflict of interest:** none

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25 commercial, or not-for-profit sectors. All medicines for the study were covered by the Hospital for
26 Children and Adolescents, Helsinki University Hospital as a part of routine patient care.

27 *Dear Editor,*

28 Zimmermann and colleagues, in this Journal, drew attention to potential changes in healthy
29 microbiota caused by ingested antibiotics. [1] We conducted a clinical trial to evaluate the efficacy
30 and safety of rectal metronidazole in the treatment of *Giardia duodenalis* (*G.duodenalis*) infection in
31 children.

32 A protozoan *G.duodenalis* infects small intestine of humans with the incubation period of 7-28
33 days. Infection can remain asymptomatic or present as diarrhea, abdominal pain or failure to thrive.
34 In Nordic countries, including Finland, prevalence of giardiasis is 5.8% in symptomatic
35 population.[2] A single positive stool enzyme immunoassay for *G.duodenalis* antigen provides a
36 diagnostic sensitivity close to 100% and specificity of >90%.[3] Nitroimidazoles represent the drugs
37 of choice for giardiasis, particularly single-dose oral tinidazole.[4] Side effects of nitroimidazoles are
38 usually mild and self-limited, including abdominal pain, nausea, diarrhea, metallic/bitter taste,
39 headache and dizziness.[4] However, oral administration of nitroimidazoles in children often proves
40 difficult in the absence of palatable pediatric formulations. Rectal tinidazole had been historically
41 used for giardiasis treatment in Finland until the drug became unavailable. Rectal metronidazole has
42 demonstrated efficacy in the treatment of vaginal trichomoniasis [5] and in the prophylaxis of
43 postoperative wound infections.[6,7] Rectal administration of metronidazole results in lower serum
44 concentrations, necessitating higher dosage.[8,9]

45 This open-label trial (ClinicalTrials.gov Identifier: NCT02942485, registered on 24th of October
46 2016) was conducted at the Children's Hospital, Helsinki University Hospital from 1.1.2017 to
47 1.11.2019. The study protocol was approved by the Institutional Ethic's Board (HUS/1065/2016) and
48 by the Finnish Medicines Agency (FIMEA, KLnro 145/2016, EudraCT 2016-001938-96). The study
49 was conducted in accordance with the Declaration of Helsinki and national and institutional
50 standards. Informed consent was obtained from the caregivers and from patients aged ≥ 7 years.

51 The Epidemiologic Operations Unit of the City of Helsinki (600 000 inhabitants) yearly
52 advertised the possibility to refer a child with giardiasis to the Children's Hospital for treatment. The

53 authors then recruited the referred children whose clinical symptoms were compatible with giardiasis
54 and whose stool samples tested positive for *G.duodenalis* in HUSLAB laboratory. Exclusion criteria
55 were: 1) age <6 months or >10 years, 2) weight <9.5 kg, 3) the absence of symptoms, and 4) co-
56 infection with another intestinal pathogen. We assessed clinical response to treatment, side effects
57 and parental acceptance of the formulation during interviews with patients/caregivers at primary visits
58 and by phone at the follow-up.

59 We randomized patients at primary visits alternately into two groups by random allocation.
60 Group 1 was treated with oral tinidazole (Fasigyn®) at a single dose of 50 mg/kg, maximum 2 g/dose.
61 Group 2 was given rectal metronidazole (Flagyl®) for three consecutive days at 500/1000/1500
62 mg/dose/day for children weighing 10-14.9/15-29.9/30-44.9 kg, respectively. The doses of rectal
63 metronidazole were arbitrary derived from the maximum oral dose (two grams) in adults. The first
64 dose of metronidazole was administered by research nurse and two subsequent doses by caregivers
65 at home. Clinical cure was defined as the resolution of symptoms by day 10 post-treatment. Stool
66 samples for enzyme immunoassay were collected on day 7-10 post-treatment. If patients did not clear
67 the infection, Group 1 was re-treated by rectal metronidazole and Group 2 by oral tinidazole (cross-
68 over). We did not measure metronidazole serum concentrations.

69 The study was terminated due to the extremely slow patient enrollment: eight patients only have
70 been referred and recruited during the two-year period (*Figure 1*). This may reflect the low prevalence
71 of giardiasis in the City of Helsinki, the inefficient advertising, or the unwillingness of primary care
72 practitioners to refer children with an easily treatable condition. At the final stage of data analysis we
73 discovered that 6/8 patients fulfilled one or more of the exclusion criteria. Four children were
74 asymptomatic, and *G.duodenalis* was detected during their routine immigrant evaluation. Five
75 patients were co-infected with other pathogens (*Shigella spp* and *Campylobacter jejuni* (n=1),
76 *Hymenolepis nana* (n=1), *Dientamoeba fragilis* (n=1) and *Blastocystis hominis* (n=4)). One
77 asymptomatic patient was excluded from further analysis due to incomplete follow-up (language
78 barrier). Thus, we next describe outcomes for six patients treated with rectal metronidazole and one

79 patient treated with oral tinidazole (*Table 1*).

80 Median age of the patients at recruitment was 2.6 years (range 1.8-6.7 years). None had chronic
81 illnesses or regular medications. All participants completed treatment without interruptions.
82 Microbiological eradication was successful after the first treatment course in 6/6 tested patients (five
83 treated with rectal metronidazole and one with oral tinidazole). All four symptomatic patients were
84 clinically cured with rectal metronidazole. For one of them (Patient 3), the follow-up stool sample
85 was unavailable. This patient's diarrhea recurred seven weeks post-treatment, and *G.duodenalis* was
86 again detected in stool sample, indicating either treatment failure or re-infection. The patient received
87 oral tinidazole with no response. After treatment with mepacrine hydrochloride according to the
88 institutional guidelines, *G.duodenalis* was eradicated and the child was clinically cured.

89 Side effects were reported in one patient as a single episode of loose stool after the third dose
90 of rectal metronidazole. The caregivers were asked to rate the ease of administration of rectal
91 metronidazole at home, according to the suggested scale (very difficult / difficult (n=1) / relatively
92 easy (n=4) / easy / very easy (n=1)). All caregivers in the rectal metronidazole group, but not the
93 caregiver of a child who had received oral tinidazole, would opt for the same treatment modality in
94 future. These results demonstrate the high rate of acceptability of rectal metronidazole by caregivers.

95 In conclusion, this is the first study evaluating the efficacy and safety of rectal metronidazole
96 in children with giardiasis. We carefully planned the open-labeled randomized comparison study,
97 which was, however, unsuccessful due to the insufficient recruitment rate. Therefore, our results are
98 observational and call for further larger trials. Despite the small sample size, and thus the descriptive
99 nature of the trial, this study provides encouraging preliminary data. We demonstrated clinical cure
100 and microbiological eradication in 4/4 and 5/5 patients with giardiasis, respectively, after a three-day
101 course of rectally administered metronidazole. Our study provides proof-of-concept for rectal use of
102 metronidazole in pediatric giardiasis.

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105 **Author contribution**

106 ES and SV designed the study. ES, TN, TSH, SB and SV recruited the patients and gathered the
107 clinical data. SV analyzed the data and drafted the manuscript. All authors contributed to the writing
108 of the manuscript and approved the final version.

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Table 1. Summary of the clinical trial of rectal metronidazole compared with oral tinidazole in children with *Giardia duodenalis* infection.

Patient	Age group at recruitment, years	Symptoms compatible with giardiasis	Treatment group	Clinical cure	Microbiological eradication	Side effects
1	1-3	abdominal pain, flatulence	rectal metronidazole	yes	yes	no
2	1-3	abdominal pain, flatulence, intermittent diarrhea	rectal metronidazole	yes	yes	loose stool once after the third dose
3	1-3	abdominal pain, diarrhea, flatulence, weight loss	rectal metronidazole	yes	n/a	no
4	1-3	none	rectal metronidazole	n/a	yes	no
5	5-8	none	rectal metronidazole	n/a	yes	no
6	1-3	intermittent diarrhea	rectal metronidazole	yes	yes	no
7	5-8	none	oral tinidazole	n/a	yes	no

n/a not applicable