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The Acute Effect of Loperamide on Ileostomy Output: A Randomized, Double-Blinded, Placebo-Controlled, Crossover Study

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Abstract: High stoma output is a common problem in patients with ileostomy and can lead to dehydration and electrolyte disturbances. The first drug of choice to reduce stoma output is often loperamide. The aim was to assess the acute effect of loperamide on (a) ileostomy output in g/day, (b) gastrointestinal transit time and (c) patient-reported effects. A total of 12 patients completed this double-blinded, randomized, placebo-controlled, crossover study, consisting of a 3-day treatment period with loperamide 12 mg/day or placebo followed by the reverse after a washout period of 5–7 days. Patients collected stoma output and noted food and fluid intake over 48 hr and swallowed a capsule with radiopaque markers for the determination of gastrointestinal transit time over 24 hr. At the end of the study, patients were asked to report their treatment sequence. Ileostomy output was significantly reduced during loperamide treatment ($p < 0.02$) with a median of 16.5% (range −5% to 46%). Transit time was reduced significantly for the passage of 10% of the markers ($p = 0.02$), but not for 50% and 100% of the markers. Fifty-eight per cent (N = 7) of the patients reported the correct treatment sequence ($p = 0.41$). Loperamide 12 mg/day reduced ileostomy output statistically significantly, but with varying effects among patients and without reaching the clinical significance of 20% set-up by this study. Dose–response studies should be performed, and standard treatment doses of loperamide should be reassessed. The study was registered at ClinicalTrials.gov – NCT02266849.

High stoma output with dehydration and/or malnutrition is common complications in patients who have an ileostomy, regardless of whether it is permanent, temporary or for diversion. The most important factors are the length and function of the remnant small intestine [1].

High output ileostomies can be difficult to manage both medically and nutritionally [2,3] and may be life-threatening for the patients [4]. Furthermore, high output can be accompanied by stoma leakage and skin problems, which may lead to social impairment and reduced quality of life [2,5–7].

High stoma output, defined as >2000 mL/day, has been reported with a frequency of up to 16% [3,8]. Other studies show that more than 60% of patients with ileostomy have signs of dehydration and electrolyte and mineral deficits [9–11], leading to dehydration as the most common reason for hospital readmission [12]. Up to 37% of patients with a high stoma output may need parenteral supplementation of nutrition and fluids [8], and more than 50% of the patients require prolonged medical treatment [8].

Gastrointestinal transit time is correlated with the amount of stoma output [13]. Loperamide has been shown to increase gastrointestinal transit time [14] and is often the primary drug of choice for treating high ileostomy output [8,15]. Previous studies indicate that loperamide reduces stoma output by ~20% [16–19]. However, clinical experience and clinical trials show that many ileostomy patients fail to respond to the recommended treatment [20,21].

The aim of this study was to investigate the effect of loperamide on (a) ileostomy output in g/day, (b) gastrointestinal transit time and (c) patient-reported outcome, in a randomized, double-blinded, placebo-controlled, crossover study.

Materials and Methods

The study was conducted as a randomized, double-blinded, placebo-controlled, crossover study from December 2014 to July 2015.

Patients were recruited for the study and assigned to the intervention by the investigator, via the stoma outpatient clinic at the Department of Surgical Gastroenterology, Odense University Hospital, Denmark. Eligible participants had to have an end or a loop-ileostomy, and be above 18 years of age. Patients with metastatic cancer and patients undergoing chemotherapy were excluded. A signed form was obtained from those who consented. Prior to inclusion, any medication with an influence on the gastrointestinal function and motility had to be discontinued for at least 2 weeks. All patients included in the study had previously and intermittently received various medications to reduce stoma output. None of the patients were dependent of intravenous support. It was not possible to obtain reliable information on remnant bowl length from the patient files.

Of a total of 331 eligible patients, 19 consented to inclusion, of which 12 patients completed the study. Patient characteristics appear in table 1.

The study was approved by the Regional Scientific Ethical Committees for Southern Denmark (S20140081), the Danish Data Protection Agency (14/23198) and the Danish Health and Medicines Authority (2014-004740-35). The trial and study protocol were registered at

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Table 1.
Patient characteristics.

Parameter	Patients (n = 12)
Sex	
Female	4
Male	8
Disease	
Ulcerative Colitis	5
Cancer	4
Intestinal ischaemia	2
Crohn's disease	1
Type of Ileostomy	
End	10
Loop	2
	Mean (range)
Age, years	64 (48–72)
Duration of ileostomy, months	34 (1–232)

ClinicalTrials.gov (NCT02266849). The local unit for Good Clinical Practice monitored the study.

The study period consisted of a 3-day period on either loperamide or placebo, followed by a washout period of 7 ± 2 days. Thereafter, the patient crossed over and proceeded with the opposite treatment for a similar length of time (fig. 1). The dosage was two capsules three times a day; each capsule contained 2 mg of loperamide or placebo.

During each treatment period, patients continued their everyday life routine without any dietary or other restrictions or recommendations. On the second day of treatment, the patients were instructed to start collecting stoma output, in appropriately labelled plastic containers provided by the Department, and note the time of the collection. The collection started at 8:00 a.m. and continued for 48 hr. At the same time, the patients were instructed to weigh (identically electronic scales – classic kitchen weight, Dansk Supermarked, Denmark) all food and fluid intake and complete a diary with the information to avoid this factor as a possible confounder. On the third day, the patients swallowed a gelatin capsule with 10 radiopaque markers (Colon Transit®, Radiopaque Markers; P. & A. Mauch, CH-4142 Münchenstein, Switzerland) at 8:00 a.m. for the determination of gastrointestinal transit time, over a period of 24 hr [22]. Patients were instructed to empty the stoma bag into consecutively numbered containers every 2 hr, for the following 10 hr, and when needed during the subsequent 14 hr. Patients noted the time of emptying on each container.

The labelled plastic containers with stoma output, collected over the 48-hr periods, were weighed twice, on the same scale as the one provided to the patients, and the average weight was calculated. Plastic containers with stoma output, collected after patients swallowed the capsule with radiopaque markers, were X-rayed to quantify the number of markers. Gastrointestinal transit time when 10%, 50% and 100% of the markers had passed through the gastrointestinal tract was noted. Finally, patients were asked whether they could guess the sequence of treatment. No further follow-up was needed.

Patients were instructed to record any adverse effects from the start of the study until 3 days after taking the last capsule. No adverse events were observed or reported by the patients.

All data were entered in a REDCap database (REDCap software – version 6.4.4. – © 2015 Vanderbilt University), which is a secure, web-based database. All data were entered as double data entry to ensure correct registration.

Loperamide 2 mg (Imolope®; Orifarm Generics, Odense, Denmark) and placebo (lactose monohydrate) were encapsulated in identical looking gelatin capsules (Capsugel®, Bornem, Belgium). The active capsules were filled with 300 mg lactose monohydrate to prevent them from rattling, thereby making it impossible for the patients to distinguish between the active and the placebo capsules.

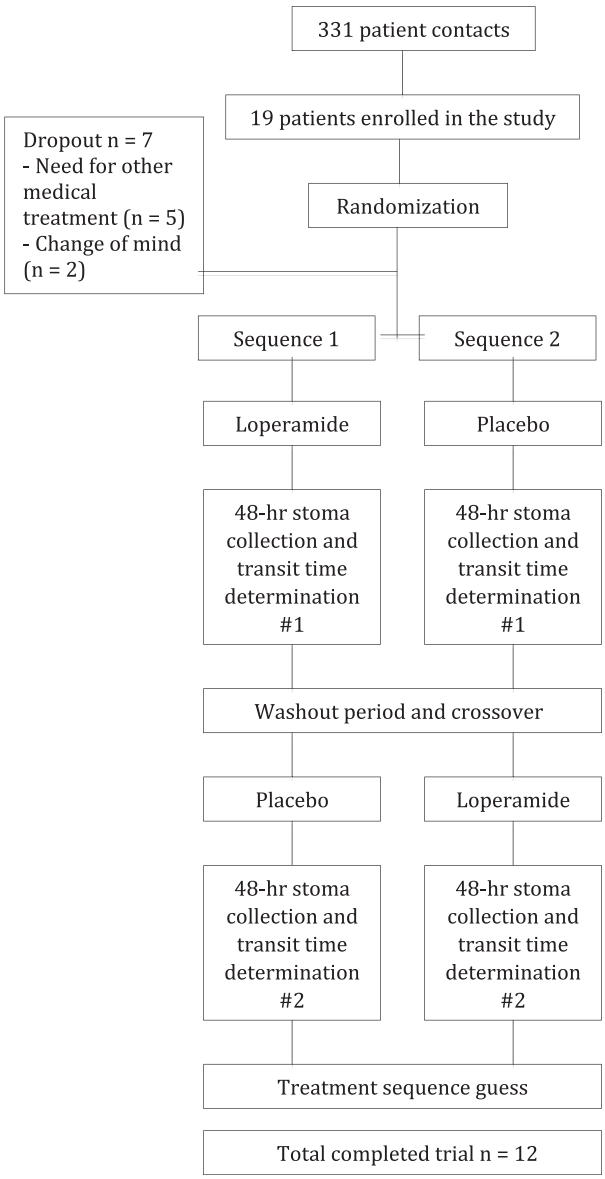

Fig. 1. Flow of the patients enrolled in the study.

The hospital pharmacy provided the allocation sequence. Randomization was computer-generated 1:1 in blocks of 4. Identical containers with coded medications were packed, sequentially numbered and consecutively dispensed to participants upon inclusion in the study. Sealed envelopes with randomization codes for each patient were stored together with the medication at the Department of Surgery, in case of adverse events demanding the allocation to be revealed. No envelopes needed to be opened in this trial, and no data collected in the study were analysed before all patients had completed the trial. Both participants and investigators were blinded to the study until all patients had completed. The allocation sequence was then requisitioned from the pharmacy.

A reduction in stoma output of 20% was considered to be at a level of clinical relevance [16–19]. With an expected S.D. of 350 g, a two-sided 5% significance level, and a power of 80% based on paired groups, a sample size of 42 events (study medication or placebo) was necessary, corresponding to the inclusion of 21 patients.

Statistical analysis was carried out in STATA® 14.0. StataCorp LLC, College Station, Texas, USA. A Wilcoxon-signed rank test was used, as the conditions of normality were unlikely to be met, to evaluate the differences in stoma output, gastrointestinal transit time and food and fluid intake during the loperamide and placebo period. Despite the data not meeting the conditions of normality, a Pearson correlation test was used to test the correlation between high stoma output during placebo treatment and the reduction in stoma output during loperamide treatment. A chi-square test was used to evaluate the patients' reports of the treatment sequence. A p-value of <0.05 was considered significant.

Results

Data from the 48-hr stoma output collection are shown in table 2 and fig. 2. The median (IQR) of the 48-hr stoma output weight was 1385.5 (651.5) grams during the placebo period, and 1147.5 (714.5) grams during the loperamide period, respectively. The median reduction in stoma output was 202.5 (451.5) grams corresponding to a median reduction of 16.5% varying from −5% to 46%. This difference was significant ($p < 0.02$). Ten of twelve patients showed a reduced stoma output. Six patients had a reduction in stoma output above 20%, and five patients had no reduction or a reduction in stoma output of <10%. No statistical differences were found in intake of food ($p = 0.7$) or fluid ($p = 0.6$) between the placebo and loperamide treatment period.

There was no correlation between high ileostomy output during the placebo period and the reduction in stoma output during loperamide treatment ($r = -0.0795$, $p = 0.8060$).

The difference in gastrointestinal transit time during the two periods for passage of 10%, 50% and 100% of the radiopaque markers is shown in table 3. A statistically significant difference was found for passage of 10% of the markers ($p < 0.02$). The median (IQR) of the transit time for passage of the first radiopaque marker was 8 (6.5) hr during the placebo treatment and 10 (8) hr during the loperamide treatment. Transit time for passage of 50% and 100% of the markers was 11.5 (15) hr and 24 (9) hr during placebo treatment and 16.5 (13) hr and 24 (4.5) hr during loperamide treatment. These differences were not significant $p = 0.40$ for 50% of the markers and $p = 1.0$ for 100% of the markers.

Seven patients reported the treatment sequence correctly and five patients reported an incorrect sequence ($p = 0.4$), as shown in table 2.

Discussion

The results of this study showed that loperamide 12 mg/day significantly reduced ileostomy output with a median of 16.5%. The effect of loperamide varied among the patients from −5% to 46%, with 40% (N = 5) of the patients having a response to loperamide of <10%, indicating that the response to loperamide was individual.

Transit time was significantly reduced during loperamide treatment when the first 10% of the radiopaque marker passed through the gastrointestinal tract, but not when measured for the passage of 50% and 100% of the markers. These results make it difficult to evaluate the effect of loperamide on gastrointestinal transit time, as also shown by some patients having very similar transit times during the two treatment periods. Some had shorter transit time during loperamide treatment. Eight patients had a transit time, for the passage of all the markers, of more than 24 hr during the placebo period, and only five patients during the loperamide treatment.

One patient had a transit time, for the passage of all markers, of more than 24 hr during placebo treatment and only 6 hr during loperamide treatment. However, the patient did have a large reduction in stoma output during loperamide treatment, indicating that gastrointestinal transit time may not be a sufficient measurement for the expected effect on stoma output, or that radiopaque markers are not the optimal measuring method [23,24]. Transit time only tells us about the actual gastrointestinal motility at the time of measurement, and it is a parameter with great intra-individual variations [24]. Other parameters need to be addressed, such as the variation in oral intake between the trial periods, which may be a more important factor for the size of the stoma output [7]. To take this

Table 2.
Results of 48-hr ileostomy output collection during the placebo and loperamide treatment period and the patients' treatment sequence guess.

Patient	Placebo output (g)	Loperamide output (g)	Difference in output (g)	Difference in output (%)	Treatment sequence guess
1	1801	1192	609	34	Correct
4	1532	1546	−14	−1	Wrong
5	4219	2454	1765	42	Correct
6	1181	931	250	21	Correct
7	1897	1742	155	8	Correct
8	1196	1103	93	8	Wrong
12	1384	928	456	33	Wrong
14	8203	8624	−421	−5	Wrong
16	1073	940	133	12	Correct
17	1387	756	631	46	Correct
18	1199	913	286	24	Correct
19	1300	1231	69	5	Wrong
Median	1385.5	1147.5	202.5	16.5	
IQR	651.5	714.5	451.5	27	

IQR, Interquartile range.

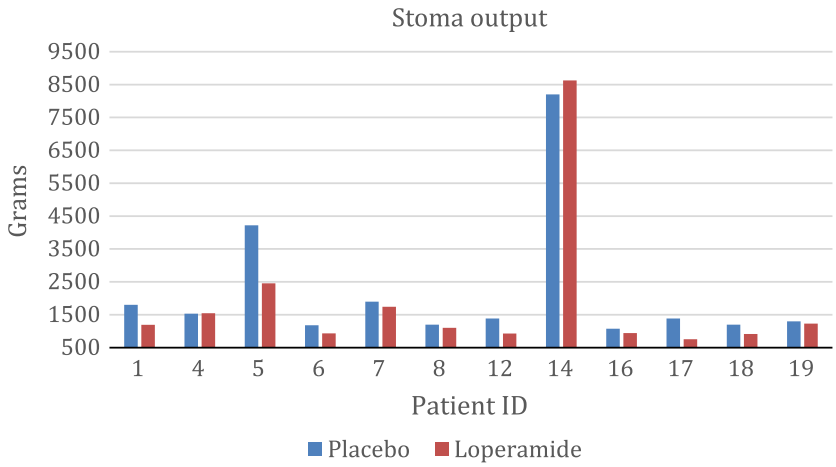

Fig. 2. Stoma output in loperamide and placebo period for each patient, $p < 0.02$.

Table 3.
Results of 24-hr gastrointestinal transit time determination during the placebo and loperamide treatment period using 10 radiopaque markers.

	Placebo			Loperamide		
Patient	Transit time 10% of the markers (hr)	Transit time 50% of the markers (hr)	Transit time 100% of the markers (hr)	Transit time 10% of the markers (hr)	Transit time 50% of the markers (hr)	Transit time 100% of the markers (hr)
1	8	8	24	16	24	>24
4	10	23	>24	17	17	>24
5	2	13	>24	2	4	6
6	16	22	>24	10	16	16
7	6	8	>24	8	18	>24
8	6	6	6	19	24	24
12	3	3	5	5	9	23
14	13	22	>24	14	23	>24
16	13	>24	>24	14	14	23
17	4	6	6	6	10	24
18	10	10	>24	10	11	14
19	8	18	>24	10	>24	>24
Median	8	11.5	24	10	16.5	24
IQR	6.5	15	9	8	13	4.5

IQR, Interquartile range.

into account, we registered all food and fluid intake during the two stoma output collection periods and no difference was found. Furthermore, other formulations for the delivery of loperamide into the upper gastrointestinal tract may be of great importance when it comes to the effect on intestinal motility. This could be investigated by testing patients' stoma output for drug residues when using different formulations. In our study, the capsules contained lactose monohydrate. It is known that lactose can affect gastrointestinal transit time. In this study, the capsules contained a very small amount 300 mg/capsule, unlikely to affect gastrointestinal transit time. In addition, both placebo and loperamide capsules contained similar amounts of lactose monohydrate.

Only 58% (n = 7) of the patients were able to report the treatment sequence correctly. The patients with the largest reduction in stoma output were more likely to report the treatment sequence correctly. Five of the six patients, with a reduction in stoma output of more than 20%, were able to report the treatment sequence correctly, whereas only two of six patients, with a reduction of stoma output of <20%, were able to report the treatment sequence correctly, indicating that a reduction <20% in output does not have a noticeable effect for the patients.

Previous placebo-controlled, double-blinded, crossover studies, containing the same data, investigated the effect of loperamide 8–12 mg/day [18,19] in 20 volunteers with ileostomy. The studies showed a 22% reduction in stoma output, and a correlation between high output during the placebo period and the reduction in output during loperamide treatment [25]. The study differed from our study by the treatment periods being longer, 7 days with loperamide, respectively, placebo, opposite 3 days in our study. Furthermore, the patients were instructed to regulate their intake of capsules with loperamide or placebo, according to their treatment response, whereas our treatment doses were constant for all the patients during all the treatment days.

Another double-blinded, placebo-controlled, crossover study [17] investigated the effect of loperamide 12 mg/day compared to codeine phosphate 180 mg/day and placebo. Ten patients were included, seven of which already required codeine phosphate treatment for the control of output. The study showed a significant reduction in stoma output during loperamide treatment. Ileostomy output was 464 (S.D. 116) g/day during loperamide treatment, compared to 633 (S.D. 253) g/day during placebo treatment. No difference was found between stoma output during loperamide treatment and codeine phosphate 524 (S.D. 200) g/day. The study consisted of 4 days with each treatment. This study also reported that patients with the highest ileostomy output benefited the most from the treatment.

The last double-blinded, placebo-controlled, crossover study [16] was performed in seven ileostomy patients and seven patients with an ileorectal anastomosis, comparing the effect of loperamide 12 mg/day with placebo. Results show a decrease in volume of stoma output among the ileostomy patients alone of 28.5%. The treatment periods of the study were 7-day loperamide/7-day placebo sequence or the reverse. This study also investigated the difference in gastrointestinal transit time during placebo and loperamide treatment without finding a significant difference.

These older studies have a similar study design to our study. One of the major differences may lie in the recruitment of patients. They do not report any information on patient recruitment, and 70% of the patients in one study [17] received other medications to reduce ileostomy output when enrolled in the study. In our study, patients were not included or excluded according to their previous response to loperamide or any other medication that may influence ileostomy output. Two of the previous studies contain the same data set [18,19]. In addition, three of the studies were performed by the same research group [16,18,19].

One of the limitations of our study was the recruitment of patients not meeting the calculated sample size of 21 patients. Many of the patients eligible for the study were elderly patients recovering from recent surgery and who did not have the energy to go through the study periods, as they found them to be complicated and time-consuming. In further studies, a simpler set-up must be considered to increase patient participation, despite a risk of less precise results. The patients most eligible for the study with a very high stoma output were more likely not to agree to inclusion into the study. They were afraid that the change in their regular medication would make their stoma output uncontrollable. We therefore had to accept patients with less stoma output for the study.

Furthermore, the study was performed by the patients themselves in their own home. To ensure optimal compliance, patients were asked, when they returned the containers with stoma output and schemes with intake, if they had followed the protocol; they were also instructed to return any leftover medication in case they had forgotten to take some of the capsules. No medication was returned.

Additional limitations were the measurement and statistical analysis of the transit time. Very few of the patients passed all of the radiopaque markers within the timeframe of systematic collection of stoma output – the first 10 hr. Therefore, analysis was performed over the whole collection period of 24 hr, knowing that without systematic collection, the actual time of passage of the radiopaque marker was unlikely to be precise. Thus, the results from the analysis of transit time should not be assigned much value. Additional radiopaque markers and more time-points for stoma collection would increase the validity of this method in further studies.

Further studies are needed to see whether it is possible to predict which patients will have the best response to loperamide. The effect should be stratified for different lengths of remaining small intestine, underlining disease and time since stoma placement. In addition, dose–response investigations are needed, as the recommended dose of a maximum of 12 mg/day is unlikely to be sufficient for a large number of the patients. Doses ranging from 24 mg/day to as much as 400 mg/day have been recommended [5,20].

In summary, loperamide 12 mg/day reduced ileostomy output, but with varying effect among the patients, and with a median of 16,5% not reaching the criteria of clinical significance of 20% set-up by this study. Thus, this suggests that loperamide treatment of ileostomy output should be based on an individual clinical assessment of each patient's treatment response. Further investigation is needed to identify which patients could experience the optimal response to loperamide. In addition, a dose–response study should be performed, and standard treatment doses of loperamide should be reassessed.

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Author Contributions

Guarantor of the article: Niels Qvist; KK and NQ designed the research study. KK performed the research, collected and analysed the data. KK and NQ wrote the article. All authors approved the final version of the manuscript.

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Disclosure Statement

All authors declare no conflict of interest.

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