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Time to treatment response of a magnesium- and sulphate-rich natural mineral water in functional constipation

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ABSTRACT

Objectives: First-line recommendations for the management of functional constipation include nutritional-hygienic measures. We previously showed that a natural mineral water rich in sulphates and magnesium (Hépar) is efficient in the treatment of functional constipation. The aim of this study was to consolidate those first results and determine a precise time to respond to Hépar.

Methods: This multicenter, randomized, double-blind, controlled study of the effect of Hépar on stool consistency and frequency in functional constipation included 226 outpatients. After washout, patients used 1.5 L of water daily, including 1 L of Hépar or of low-mineral water, during 14 d. In addition to a daily reporting of stool consistency by the patient, an expert investigator blindly analyzed stool consistency (Bristol stool scale) based on photographs taken by the patient.

Results: The primary endpoint was met. Treatment response was more frequent in the Hépar arm than in the control group at day 14 (50% versus 29%, respectively; $P = 0.001$). Mean time to treatment response was shorter in the Hépar group (6.4 d) than in the control arm (7.3 d; $P = 0.013$). Concomitant stool scoring was available for 60% of the patients. Scores given to 79% of the stools were similar between the patient and the expert (differences ≤ 1). Safety analyses showed excellent results.

Conclusion: This study confirms the efficacy and safety of Hépar in the treatment of functional constipation and shows that it is associated with a response within 7 d. Hépar could be a safe response to the current absence of first-line medication in the treatment of functional constipation.

Introduction

Chronic constipation has an estimated prevalence of 14% (around 20% in France) and is twice as more frequent in women than in men [1–3]. It is associated with a major effect on patients' quality of life and high health care and other indirect costs [4,5].

First-line recommendations are lifestyle changes, therapeutic education, and nutritional-hygienic measures including 15 to 40 g/d fiber and sufficient water intake [2,6]. In 2013, we performed a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the magnesium- and sulphate-rich natural mineral water Hépar in women outpatients with functional constipation according to the Rome criteria III [7]. No significant effect was observed at week 1 (primary criterion) but constipation was significantly reduced after 2 wk of 1 L/d Hépar. The 1 L Hépar group also showed very good safety, a decreased number of hard or lumpy stools (Bristol stool scale, $P = 0.030$ versus baseline), and a substantial decrease in the use of rescue medication ($P = 0.034$ versus controls). Patient response correlated with magnesium and sulphate concentrations. However, that 4-wk study could not allow determining the precise delay until response to the treatment (between 1 and 2 wk). Additionally, stool consistency was estimated using the Bristol stool scale, based on the sole patient declaration, which could question validity of this measurement.

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The present study aimed to determine the precise delay until response to 1 L/d of Hépar and confirm previous results [7]. In addition, this study included a parallel stool ranking (Bristol stool scale) by an expert physician using photographs taken by the patient.

Methods

Study design

This was a multicenter, comparative, randomized, double-blind, placebo-controlled study to confirm efficacy of the daily consumption of 1 L/d of Hépar for 14 d in constipated outpatients.

Secondary objectives were to assess the mean time to response to the daily consumption of 1 L of Hépar, and the effect of 1 L Hépar on stool frequency and consistency, abdominal pain, and Rome III criteria.

Participants

Healthy patients meeting all of the following criteria were included in the study:

- Female outpatients ages 18 to 60 y;
- Having diagnosis of functional constipation according to the Rome III criteria [8];
- Not using any laxative drug for 3 d before screening;
- Having easy access to toilet;
- Regularly eating vegetables and fruits;
- Participating in physical activity, reasonable walking periods, or exercise twice or three times a week; and
- Drinking 1. 5 ± 0.5 L/d of water.

Patients who presented any of the following criteria were excluded from the study:

- Known dissatisfaction with Hépar;
- Treatment or disease (current or past) likely to interfere with evaluation of the study parameters; and
- Documented pregnancy.

The study was conducted by 28 city-based general practitioners located throughout France.

Interventions

After a screening visit, patients followed a washout period during 7 to 9 d before study inclusion. Patients had to stop any drug treatment that would interfere with transit and drink 1.5 L/d of a low-mineral spring water (Nestlé Purelife, Nestlé Waters, France). At the inclusion visit, patients were randomized to the control or Hépar group according to the chronological order of inclusion and to a predetermined randomization list in balanced blocks of four treatment units (SAS software; SAS Institute, Cary, NC, USA). The randomization list was prepared in advance by the statistician from the society in charge of the logistic of bottles and secured in an electronic file with restricted access. Two sets of sealed envelopes kept by the investigator and the study manager in a secure and locked place were generated to contain the patient's randomization number and allocated group. The investigator could break the blinding in case of absolute emergency and in accordance with the sponsor. The follow-up visit was performed 15 to 17 d after inclusion.

Patients had to drink 1.5 L/d from days 1 to 14. Depending on the randomization, they drank either 1.5 L of low-mineral water (Vittel Bonne Source, control group) or 1 L of Hépar + 0.5 L of low-mineral water (Hépar group). An additional 0.5 L of low-mineral spring water was allowed for patients who were used to consuming ≥2 L/d of water on average at baseline. Patients could have other sources of water including vegetables, fruits, soup, and cold or hot beverages.

The Hépar total mineralization is 2513 mg/L (calcium 549 mg/L; magnesium 119 mg/L; sulphate 1530 mg/L; sodium 14.2 mg/L; potassium 4.1 mg/L; bicarbonate 383.7 mg/L; nitrate 4.3 mg/L). Its pH is 7.2 at 23°C. Hépar is currently marketed in France at the mean observed cost of 0.52€/L (0.58 US$/L; IRI, in retail, year-to-date October 2016). Control product was a natural low-mineral water (Vittel Bonne Source [BS]), with total mineralization of 400 mg/L (calcium 94 mg/L; magnesium 20 mg/L; sulphate 120 mg/L; sodium 7.7 mg/L; potassium 5 mg/L; bicarbonate 248 mg/L; nitrate <0.5 mg/L). Hépar and the control product were contained in identical 1 L bottles plus a second 0.5 L bottle of Vittel BS. Both patient and physician were blind to the treatment.

If abdominal pain became greater than 70 on a 100-mm visual analog scale (VAS), rescue medication (i.e., two sachets of 10 g macrogol 4000/d) was authorized until return to the basal abdominal pain level.

Measurements

During the screening visit (V0), the physician collected sociodemographic characteristics, previous medical history and history of the constipation episode (Rome III criteria), onset of symptoms, abdominal pain on a 100-mm VAS, dietary habits, physical activities, and previous and current treatments. The patient was provided with a self-evaluation via an e-diary to collect the following information:

- the number and type of stools (Bristol stool scale) [9];
- abdominal pain rating during the previous 24 h;
- physical activity; and
- drug, water, beverage, and food consumption during washout.

At inclusion (V1), the physician collected information on the following:

- the weekly number and type of stools;
- Rome III criteria;
- patient's ability to complete the e-diary;
- patient compliance with the washout treatment (count of unused bottles); and
- patient's use of rescue medication over the previous week.

During the final visit (V2), the physician collected information on the following:

- the weekly number and type of stools;
- Rome III criteria;
- adverse events (AEs);
- patient compliance with the treatment (count of unused bottles); and
- patient's use of rescue medication over the previous 2 wk.

For the washout and the treatment periods, the type of stool was assessed directly by the patient on the e-diary (Bristol stool scale) [9] and also was analyzed blindly by an expert investigator (Bristol stool scale). The expert performed a blind review of stool consistency based on photographs taken by patients of each of their stools. These photographs were made accessible through an online database. Both evaluations from the patient and the expert were performed according to the Bristol stool scale, which classifies stools in seven types, with type 1 and 2 indicating marked constipation; types 3, 4, and 5 indicating normal stool form; and types 6 and 7 indicating diarrhea. Pictures not clear enough to allow analyze were not considered by the expert.

Outcomes

The primary endpoint was the response to a 2-wk 1 L/d Hépar water consumption. It was evaluated using a composite variable based on two separate components of the Rome III criteria:

- ≥4 stools per week or an increase of ≥2 stools as compared with baseline and
- <25% of lumpy or hard stools, as reported by the patient.

Both of these criteria were required to consider a patient had responded to treatment.

Secondary endpoints were as follows:

- defecation frequency;
- stool consistency (Bristol stool scale);
- individual and total Rome III diagnostic criteria for functional constipation (Table 1);
- abdominal pain (VAS);
- use of rescue medication; and
- safety (reports of AEs).

Sample size calculation

The number of participants required was calculated based on a unilateral test with an α-risk level of 0.05 and a statistical power of 90%. The hypotheses were based on the results of a previous study [7], which showed 16.4% more responders

Table 1
Rome III scoring according to the frequency of symptoms over the 2 wk preceding measurement

Variables	Frequency	Score
Abdominal discomfort or pain	Never	0
	<1 d/mo	1
	Once a month	2
	2 or 3 d/mo	3
	1 d/wk	4
	>1/wk	5
	Every day	6
Discomfort or abdominal pain improved after defecation		
Straining during defecation	Never or rarely	0
Sensation of incomplete evacuation after defecation	Sometimes	1
Sensation of anorectal obstruction/blockage	Often	2
Manual maneuvers to facilitate defecation	Most of time	3
Difficulty relaxing to allow stool evacuation	Always	4
Hard stools		
Soft or liquid stools	Never or rarely	4
	Sometimes	3
	Often	2
	Most of time	1
	Always	0
Maximum total score		38

in the Hépar arm than in the control group (37.5% versus 21.1%, respectively). The number of patients needed was 131 per group (262 completing the study). Anticipating 10% dropouts, 286 patients had to be included. Intermediate analyses were performed by an independent statistician to re-estimate the number of needed participants after 55% of the expected patients were included (n = 79 in each group). The number of participants was estimated at 101 patients per group.

Statistical analyses

The primary endpoint was analyzed in the intent-to-treat (ITT) population, which included all the randomized patients evaluable for the primary endpoint. The per-protocol (PP) population included randomized patients without major deviation to the protocol. The modified per-protocol (PP+) population included patients from the PP population for whom expert stool rating was available for ≥80% of the stools.

Quantitative variables are described using mean and SD and compared using the Student's t test for normally distributed variables (Shapiro–Wilk test). Non-normally distributed variables were compared using the Wilcoxon test. Qualitative variables are described using number and percentage and compared using the χ^2 or Fisher exact tests. The time to become responder was described using Kaplan–Meier curves and compared using the log-rank test. Evolution of abdominal pain was analyzed using analysis of covariance (ANCOVA). The level of significance was set at $\alpha = 0.05$. The correlation between the expert's and the patient's evaluation of stool consistency was analyzed using weighed κ coefficient, adjusted on concordance level.

Statistical analyses were two-sided and performed using the SAS software, version 9.4 (SAS Institute).

Ethics

All the patients provided signed informed consent. The protocol was approved on September 5, 2014 by local French ethics committee and the French Regulatory Agency. It was conducted in accordance with the principles of the Helsinki Declaration and its subsequent amendments and in accordance with Good Clinical Practice.

As the tested product was not a health care product, no registration to a clinical trial registry was required before enrolment of the participants. The study was registered to clinicaltrials.gov on November 13, 2017.

Results

Population

As illustrated in Figure 1, we assessed 232 women for eligibility and randomized 226 between December 2014 and June 2016. The ITT population comprised 111 patients in the control group and 110 patients in the Hépar group. Mean (±SD) age was 41.4 ± 11 y, mean height 163.9 ± 6.3 cm, and mean weight 65.5 ± 13.5 kg (Table 2). Mean Rome III score was 18.5 ± 4.5 in the control group and 18.2 ± 4.8 in the Hépar group. The scores corresponded to mild constipation in 80.8% and moderate constipation in 19.2% of the patients. At inclusion, patients from both groups also had similar physical activity, fluid consumption, and medical characteristics. No modifications were observed regarding physical activity or fluid consumption during the study.

Treatment compliance was very good: 93.4% ± 10.8% in the Hépar group and 93.1% ± 9.9% in the control group, which corresponded to a mean duration of consumption of 14 ± 0.9 and 14 ± 0.7 d, respectively, and a mean consumption of 1.4 ± 0.2 L/d in both groups.

Efficacy outcomes

The primary endpoint was met as the proportion of responders at day 14 was higher in the Hépar (50%) than in the control group (28.8%; $P = 0.001$; Table 3). These results observed in the ITT population were also observed in the PP (42.9% versus 26.6%; $P = 0.02$) and PP+ populations (36.1% versus 12.5%; $P = 0.02$). This was associated with a higher frequency of stool output (in the ITT 0.9 ± 0.7 versus 0.7 ± 0.7 stools/d, $P = 0.02$) and a lower proportion of grade 1 to 2 stools in the Hépar arm than in the control group (19.4% versus 32.7%, $P = 0.03$), as recorded by the patients.

The mean time to response to treatment was shorter in the Hépar than in the control group (respectively, 6.4 ± 0.6 and 7.3 ± 0.5 d, $P = 0.013$).

Stool grading according to the Bristol stool scale was performed for each individual stool by both the patient and by an expert physician from photographs taken by the patient. From 2818 stools, 2079 photographs (73.8%) were received and 1685 stools (59.8%) had both scorings. Expert assessment was more severe in 46.4% of the cases, patient assessment was more severe in 20.4% of the cases, and both estimations were identical for 33.4% of the photographed stools (Table 4). However, 78.8% of the stools had a difference in the respective rankings ≤1. The weighed κ coefficient of correlation was 0.40 ($P < 0.0001$) between the patient's and the expert's evaluation.

In all, 202 patients (102 in the control group and 100 in the Hépar group, $P = 0.46$) provided photographs for ≥25% of their stools. Of the 17 patients who did not, 10 did not provide any photograph. No significant difference was observed between patients who provided ≥25% of photographs and those who provided <25% (Table 5).

Abdominal pain and other variables

Abdominal pain was estimated daily by the patient and by the physician at inclusion (Table 2) and at day 14 (Table 3). According to the results provided by the physician, no difference was observed between groups at day 14. On the contrary, the daily reporting by the patient showed that abdominal pain was significantly more reduced in the Hépar than in the control group at day 14 (VAS: −11.3 ± 25.7 versus −2.2 ± 27.7, respectively; $P = 0.002$). The use of rescue medication did not differ significantly between groups during follow-up ($P = 0.28$).

Because the number of recruited patients substantially differed between centers (from 1 to 30), a statistically significant center effect was observed in univariate analysis (Wald test, $P = 0.005$). However, the weight of this effect did not significantly affect the results of the study ($P = 0.998$).

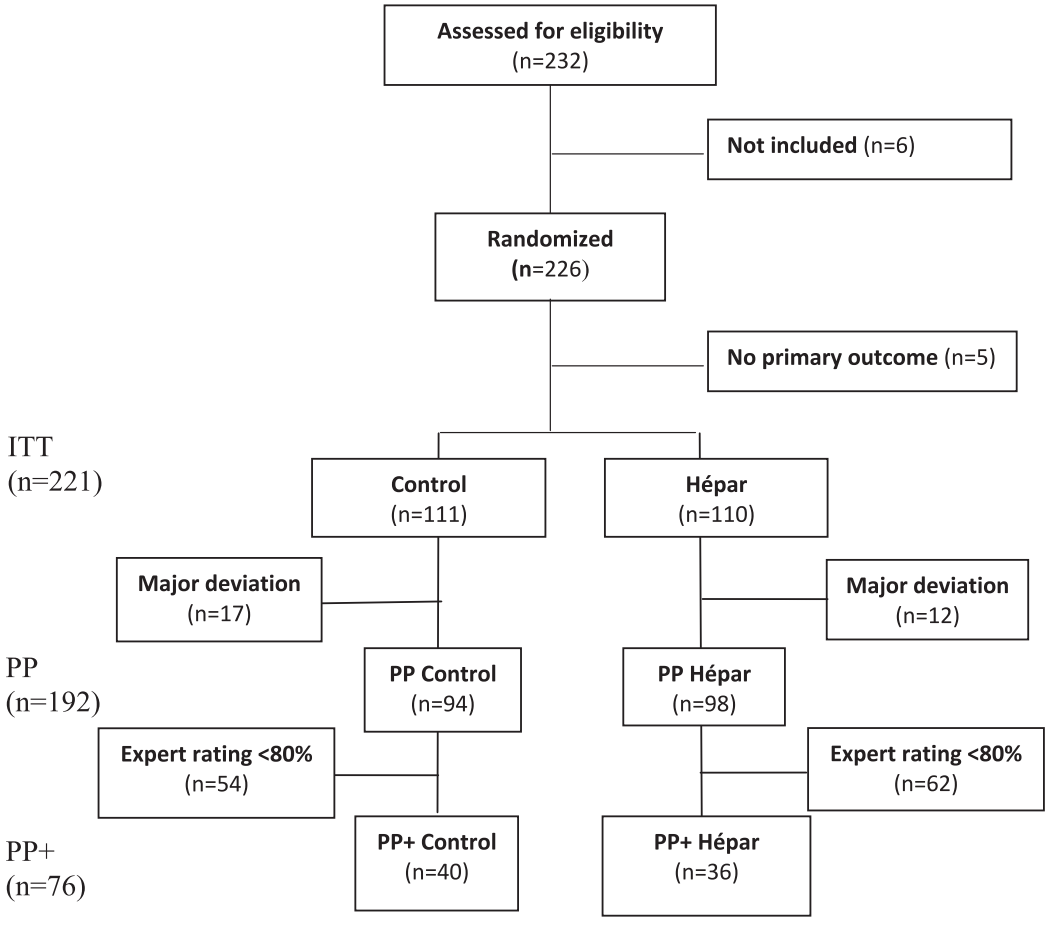

Fig. 1. Flow chart of the patients. ITT, intent-to-treat; PP, per protocol; PP+, modified per protocol.

Safety

The safety was assessed on 222 patients, 111 in each group. Seventeen patients reported 20 AEs during the study: 5 patients in the control group (7 AEs) and 12 in the Hépar group (13 AEs). These were eight seasonal infectious diseases, five abdominal pain or ballooning, and two headaches. It was estimated that only two of these AEs could be related to the treatment, both in the Hépar group (abdominal bloating and meteorism).

Table 2
Patients' characteristics at inclusion (V1) (ITT population)

	Control n = 111	Hépar n = 110	Total N = 221
Age (y), mean ± SD	41.3 ± 10.6	41.4 ± 11.4	41.4 ± 10.9
Height (cm), mean ± SD	164 ± 7	163.7 ± 5.6	163.9 ± 6.3
Weight (kg), mean ± SD	66 ± 14.3	64.9 ± 12.5	65.5 ± 13.5
BMI (kg/m^2), mean ± SD	24.5 ± 5.2	24.3 ± 4.8	24.4 ± 5
Abdominal pain (VAS), mean ± SD	34.2 ± 24.9	32.5 ± 23.8	33.3 ± 24.3
Rome III score			
Mean ± SD	18.5 ± 4.5	18.2 ± 4.8	18.4 ± 4.7
Severity, n (%)			
Mild, ≤22	89 (82.4)	83 (79)	172 (80.8)
Moderate, 23–34	19 (17.6)	22 (21)	41 (19.2)
Severe, ≥35	0 (0)	0 (0)	0 (0)

BMI, body mass index; ITT, intent-to-treat; VAS, visual analog scale.

Discussion

This study was designed to assess time to treatment response of Hépar in the treatment of functional constipation and ascertain the results of the previous study we performed on the efficacy and safety [7]. It showed a mean time to treatment response of 6.4 d and confirmed that Hépar is an efficient and safe treatment for functional constipation. The use of stool photographs blindly analyzed by an expert investigator was an innovation and proved to be rather efficient because similarity between patients' and expert's grading reached 79%.

Recruitment paid particular attention to focusing on functional constipation. To avoid irritable bowel syndrome with constipation, patients for whom abdominal pain was the dominant symptom were not included [10]. Accuracy was substantiated by the use of an e-diary to be completed daily instead of weekly in the first study, and by the use of photographs taken by the patients for each stool, with further analysis by a blinded investigator [11]. When launching the study, we anticipated that this requirement might be difficult to accept by the patients, which was not the case because a photograph was available for 74% of the stools. Additionally, patients sending photographs for <25% of their stools did not show any significant difference with the other patients. The use of photographs taken by the patients appeared not to induce any substantial bias.

Table 3
Response to the 14-d treatment with a low-mineral water or 1 L Hépar daily (visit 2)

	ITT population			PP population			PP+ population		
	Control n = 111	Hépar n = 110	P-value	Control n = 94	Hépar n = 98	P-value	Control n = 40	Hépar n = 36	P-value
Responders to the treatment, n (%)	32 (28.8)	55 (50)	0.001	25 (26.6)	42 (42.9)	0.018	5 (12.5)	13 (36.1)	0.016
Stool frequency (n/d), mean ± SD	0.7 ± 0.7	0.9 ± 0.7	0.019	0.6 ± 0.7	0.8 ± 0.7	0.039	0.6 ± 0.7	0.7 ± 0.6	0.37
Stool consistency, n (%)			0.037			0.072			0.661
Grade 1–2 (hard or lumpy)	17 (32.7)	14 (19.4)		17 (34)	14 (20.9)		9 (42.9)	6 (26.1)	
Grade 3–5 (normal)	34 (65.4)	52 (72.2)		32 (64)	49 (73.1)		11 (52.4)	16 (69.6)	
Grade 6–7 (loose or liquid)	1 (1.9)	6 (8.3)		1 (2)	4 (6)		1 (4.8)	1 (4.3)	
Rome III score, mean ± SD	12.3 ± 5.8	12.3 ± 6	0.97	12.7 ± 5.6	11.9 ± 5.6	0.31	12.2 ± 5.3	12.1 ± 6.2	0.90
Abdominal pain (VAS), mean ± SD									
At day 14 (visit 2)	32.5 ± 27.1	21.2 ±22		32.4 ± 26.8	21.5 ± 22.5		26.8 ± 25.2	22.2 ± 23.9	
Mean individual evolution since inclusion	−2.2 ± 27.7	−11.3 ± 25.7	0.002*	−1.9 ± 27	−11.3 ± 26.1	0.002	−2.5 ± 27	−7.1 ± 23.9	0.36
Use of rescue laxatives during follow-up, n (%)	25 (23.1)	19 (17.3)	0.28	21 (22.3)	14 (14.3)	0.15	11 (27.5)	4 (11.1)	0.073

ITT, intent-to-treat; PP, per protocol; PP+, modified per protocol; VAS, visual analog scale.
*Repeated measures non-parametric analysis of covariance.

Another question related to the possibility of substantial discrepancy in stool grading between patients and the expert. The expert, used to severe cases of constipation, might provide an evaluation less severe than that of the patient [12]. Actually, more severe ranking was twice as more frequent with the expert. Patients were not specifically trained to use the Bristol stool scale or might tend to underestimate their perception when having to really declare it to a third party. The coefficient of correlation between the expert's and the patient's assessment was only 0.4 but such coefficients are strongly influenced by extreme values [13]. Some of these extreme values were most probably due to an error in the way of quotation as some results differed by 6 points over a total of 7. Nonetheless, 79% of the evaluations were identical or varied by no more than 1 point between the expert and the patient. Additionally, the use of photographs allows studying outpatients' response to the treatment in their daily living, which provides a better image of the actual efficiency of the treatment.

Response to the treatment was observed in 50% of the patients in the Hépar group versus 29% in the control group (P = 0.001). That difference in the proportion of responders between groups (i.e., 21%) is close to the figure we reported in the first study (16%). The higher efficacy of 1 L/d Hépar during 2 wk in the treatment of functional constipation was observed in ITT, PP, and PP+ populations.

The mechanism of action of such a mineral water is most probably related to its high content in magnesium and sulfate [14–19]. In addition to an osmotic effect retaining water in the intestinal lumen, due to the moderate intestinal absorption of magnesium and sulfate, additional mechanisms have been suggested including increased release of cholecystokinin and activation of the nitric oxide synthase [20], and expression of the aquaporin-3 transport protein [21].

Table 4
Difference* between patient and expert stool scoring on the 7-grade Bristol stool scale: N = 1685 photographs

	Difference	N (%)
More severe patient evaluation than expert evaluation	−4	5 (0.3)
	−3	25 (1.5)
	−2	75 (4.5)
	−1	237 (14.1)
Identical evaluations	0	562 (33.4)
More severe expert evaluation than patient evaluation	+1	528 (31.3)
	+2	154 (9.1)
	+3	70 (4.2)
	+4	27 (1.6)
	+5	1 (0.1)
	+6	1 (0.1)

*Difference = figure provided by the patient − figure provided by the expert.

The present study intended both to confirm the previous one and to precisely determine the time to treatment response. In the first study, a significant response after treatment initiation was not reached at 1 wk but at 2 wk, meaning that the effect occurred during the second week. Weekly assessments did not allow sufficient precision, and higher granularity was the prerequisite to determine treatment response on a daily basis. We thus used daily data recording from e-diaries to allow Kaplan–Meier survival analysis and showed a mean time to treatment response of 6.4 d with Hépar, which is shorter than with controls ($P = 0.013$). These results confirm that the consumption of 1 L/d Hépar significantly shortens mean time to obtain treatment response. Altogether, results from the first and the second study suggest in patients responding to treatment that the effect occurred grossly after 1 wk. The use of e-diaries and stool photographs in this outpatient population contributed to more accurately showing the effect of Hépar on daily life.

Hépar is highly mineralized and has a characteristic taste. It is an easily available mineral water largely known in France for its beneficial effect in constipation. Some or all of the patients likely had already tried Hépar to improve their symptoms of constipation. As a consequence, at least some of the patients may have been aware of the group to which they had been assigned. This might have affected the results we observed between the Hépar

Table 5
Characteristics at inclusion and response to treatment at day 14 (visit 2)*

	<25% n = 17	≥25% n = 202	Total N = 219	*P*-value
Age (y), mean ± SD	38.6 ± 9.7	41.5 ± 11	41.2 ± 10.9	
Height (cm), mean ± SD	162.4 ± 8.6	163.6 ± 6.1	163.9 ± 6.3	
Weight (kg), mean ± SD	69.8 ± 12.5	65.1 ± 13.5	65.4 ± 13.5	
BMI (kg/m^2), mean ± SD	26.4 ± 4.9	24.2 ± 4.9	24.4 ± 5	
Abdominal pain (VAS), mean ± SD	36.9 ± 24.2	33.2 ± 24.3	33.5 ± 24.3	
Rome III score				
Mean ± SD	19.4 ± 4.5	18.3 ± 4.7	18.4±4.7	
Severity, n (%)				
Mild, ≤22	13 (81.3)	158 (80.6)	171 (80.7)	
Moderate, 23–34	3 (18.8)	38 (19.4)	41 (19.3)	
Severe, ≥35	0 (0)	0 (0)	0 (0)	
Responder to the treatment, n (%)†	8 (47.1)	79 (39.1)	87 (39.7)	0.520
Stool frequency (n/d), mean ± SD†	0.9 ± 0.6	0.8 ± 0.4	0.8 ± 0.5	0.9158

BMI, body mass index; ITT, intent to treat; VAS, visual analog scale.
*Results presented for patients providing photographs for <25% or ≥25% of their stools (ITT population).
†At visit 2.

and placebo groups. Nevertheless, the way this effect occurred is not simple to determine [22].

A placebo effect can be easily imagined. Patients being aware of their attribution to the Hépar group may have anticipated an improvement of their symptoms. However, a nocebo effect also could be imagined. Patients were recruited in a French general practitioner setting, during a consultation related to their chronic functional constipation. These patients who came to see a general practitioner for their constipation most probably already tried Hépar and estimated that the consumption of this mineral water was not sufficient for them. As a consequence, it may be hypothesized that some of the patients assigned to the Hépar group might have had a negative opinion of the efficacy of this mineral water for the treatment of their constipation. This may have resulted in a nocebo effect and a lowered efficacy of Hépar in this study. Moreover, a nocebo effect also could have occurred in the placebo group patients who were aware of their attribution in this group. This would have induced a worsening of the symptoms of constipation in the placebo group during the interventional period, which we did not observe. Therefore, we believe that the placebo and nocebo effects that may have occurred in this study were marginal and unlikely responsible for the significant difference we observed.

The current recommendations for functional constipation start with lifestyle changes, physical activity, education, and nutritional-hygienic measures (e.g., sufficient fiber consumption and water intake) [5,6,23–25]. Consumption of a water rich in minerals (especially in magnesium) is progressively taken into account [26]. The consumption of Hépar, with its specific magnesium and sulphate contents, is now supported as a first-line treatment of functional constipation by this study and the previous one [7]. This natural mineral water has been marketed for more than a century without any question regarding its safety, which clinical studies confirm. Efficacy and safety of 1 L/d of Hépar support its use as a first-line treatment of functional constipation before considering drug therapy.

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