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

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Short Title: Hépar in functional constipation

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Abstract

Objective: The 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 present study aimed at consolidating those first results and determining a precise time to response to Hépar.

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

Results: The primary endpoint was met. Treatment response was more frequent in the Hépar than in the control group at day 14 (respectively 50% vs. 29%, p=0.001). Mean time to treatment response was shorter in the Hépar (6.4 days) than in the control group (7.3 days) (p=0.013). Concomitant stool scoring was available in 60% of the patients. 79% of the stools had similar scores by 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 days. Hépar could be a safe response to the current absence of first-line medication in the treatment of functional constipation.

Keywords: Bowel movement; Functional constipation; Clinical trial; Natural mineral water; Treatment.

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 high impact on patients' quality of life, and high healthcare and other indirect costs (4, 5).

First-line recommendations are lifestyle changes, therapeutic education and nutritional-hygienic measures including 15-40 g fibres per day and sufficient water intake (2, 6). In 2013, we performed a first 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 weeks of 1L Hépar daily. The 1L Hépar group also showed very good safety, a decreased number of hard or lumpy stools (Bristol scale, $p=0.030$ vs baseline) and a substantial decrease in the use of rescue medication ($p=0.034$ vs controls). Patient response correlated with magnesium and sulphate concentrations. However, that 4-week study could not allow determining the precise delay until response to the treatment (between 1 and 2 weeks). In addition, stool consistency was estimated using the Bristol scale, based on the sole patient declaration, which could question validity of this measurement.

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

Methods

Study design

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

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

Subjects

Healthy patients meeting all of the following criteria were included in the study: i) female outpatient aged 18 to 60, ii) with a diagnosis of functional constipation according to the Rome III criteria (8), iii) without any laxative drug for 3 days prior to screening, iv) having easy access to toilet, v) regularly eating vegetables and fruits, vi) having physical activity, reasonable walking periods or exercise 2 or 3 times a week and vii) drinking 1.5±0.5L of water /day. Patients who presented any of the following criteria were excluded from the study: i) known unsatisfaction to Hépar, ii) concomitant treatment or disease (current or past) likely to interfere with evaluation of the study parameters and iii) 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 days before study inclusion. Patients had to stop any drug treatment liable to interfere with transit and drink 1.5 litres per day 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 4 treatment units (SAS® software). 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 days following inclusion.

Patients had to drink 1.5L water per day from day 1 to day 14. Depending on the randomization, they drank either 1.5L of low-mineral water (Vittel Bonne Source, control group) or 1L of Hépar + 0.5L of low-mineral water (Hépar group). An additional 0.5L of low-mineral spring water was allowed for patients who were used to consume ≥ 2L of water per day 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 2513mg/L (calcium 549 mg/L; magnesium 119mg/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 (IRI, in retail, Year-to-date October 2016). Control product was a natural low-mineral water (Vittel Bonne Source (BS)), which total mineralization is 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 Control product were contained in identical 1L bottles plus a second 0.5L bottle of Vittel BS. Both patient and physician were blind to the treatment.

If abdominal pain became higher than 70 on a 100 mm visual analogic scale (VAS), rescue medication (i.e. 2 sachets of 10g macrogol 4000/day) was authorized until return to the basal abdominal pain level.

Measurements

During the screening visit (V0), the physician collected sociodemographics, 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: i) the number and type of stools (Bristol Scale) (9); ii) abdominal pain rating during the last 24 hours, iii) physical activity and iv) drug, water, beverage and food consumption during washout.

At inclusion (V1), the physician collected: i) the weekly number and type of stools, ii) Rome III criteria, iii) ability to complete the e-diary, iv) compliance to the washout treatment (count of unused bottles), and v) use of rescue medication over the past week.

During the final visit (V2), the physician collected: i) the weekly number and type of stools, ii) Rome III criteria, iii) AEs, iv) compliance to the treatment (count of unused bottles) and v) use of rescue medication over the past two weeks.

For the washout and the treatment periods, the type of stools was assessed directly by the patient on the e-diary (Bristol scale) (9) and, secondarily, blindly analysed by an expert investigator (Bristol scale). This expert performed a blind review of stool consistency based on photographs taken by the patients for 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 scale, which classifies stools in seven types, type 1 and 2 indicating marked constipation, types 3, 4 and 5 as normal stool form and types 6 and 7

indicating diarrhoea. Pictures not clear enough to allow analyse were not considered by the expert.

Outcomes

The primary endpoint was the response to a two-week 1L/day Hépar® water consumption. It was evaluated using a composite variable based on two separate components of the Rome III criteria: i) 4 stools or more per week, or an increase of 2 stools or more as compared to baseline, and ii) less than 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: i) defecation frequency; ii) stools consistency (Bristol scale); iii) individual and total Rome III diagnostic criteria for functional constipation (Table 1); iv) abdominal pain (VAS); v) use of rescue medication and vi) Safety (reports of AEs).

Sample size calculation

The number of subjects 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 our previous study (7), which showed 16.4 percentage points more responders in the Hépar than in the control group (37.5% vs 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 in order to re-estimate the number of needed subjects, after 55% of the expected patients were included (n=79 in each group). The number of subjects was estimated to 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 standard deviation (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 Chi2 or Fisher exact tests. The time to become responder was described using Kaplan-Meier curves and compared using the Logrank 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 analysed using weighed kappa coefficient, adjusted on concordance level.

Statistical analyses were two-sided and performed using the SAS® software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

All the patients provided signed informed consent. The protocol was approved on September 05, 2014 by local French ethics committee and the French Regulatory Agency (ANSM: *Agence Nationale de Sécurité du Médicament et des Produits de Santé*). It was conducted in accordance with the principles of the Helsinki Declaration and its subsequent amendments, and in accordance with Good Clinical Practice (CPMP/ICH/135/95).

As the tested product was not a healthcare 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 under the identifier NCT03348007.

Results

Population

As illustrated in the flow chart presented in Figure 1, 232 female patients were assessed for eligibility and 226 randomized 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 years, 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. It 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 ± 0.9 and 14.0 ± 0.7 days, respectively, and a mean consumption of 1.4 ± 0.2L per day in both groups.

Efficacy outcomes

The primary endpoint was met since the proportion of responders at D14 was higher in the Hépar (50.0%) 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% vs. 26.6%; p=0.02) and PP+ populations (36.1% vs. 12.5%; p=0.02). This was associated with a higher frequency of stools output (in the ITT 0.9 ± 0.7 vs 0.7 ± 0.7 stools/day, p=0.02) and a lower proportion of grade 1-2 stools in the Hépar than in the control group (19.4% vs. 32.7%, p=0.03), as recorded by the patients.

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

Stool grading according to the Bristol scale was performed for each individual stool by both the patient and by an expert physician from photographs taken by the patient. From a total of 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 lower or equal to 1. The weighed kappa coefficient of correlation was 0.40 ($p<0.0001$) between the patient's and the expert's evaluation.

A total of 202 patients (102 in the control group and 100 in the Hépar group, p=0.46) provided photographs for at least 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 patients 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 D14 (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 vs -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 centres (from 1 to 30), a statistically significant centre 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).

Safety

The safety was assessed on 222 patients, 111 in each group. A total of 17 patients reported 20 adverse events (AEs) during the study: 5 patients in the control group (7 AEs) and 12 in the Hepar group (13 AEs). These were 8 seasonal infectious diseases, 5 abdominal pain or ballooning and 2 headaches. It was estimated that only 2 of these AEs could be related to the treatment, both in the Hépar group (abdominal bloating and meteorism).

Discussion

This study was designed to assess time to treatment of Hepar 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 days and confirmed that Hépar is an efficient and safe treatment of functional constipation. The use of stool photographs blindly analysed by an expert investigator was an innovation and proved to be rather efficient since similarity between patients' and expert's grading reached 79%.

Recruitment paid a particular attention to focusing on functional constipation. In order to avoid IBS-C, 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 filled-in 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 since a photograph was available for 74% of the stools. In addition, patients sending photographs for lower than 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.

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 scale and/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 since 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. In addition, 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 1L Hépar per day during two weeks 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 (AQP)-3 transport protein (21).

The present study intended both to confirm the previous one and to precisely determine the time to treatment response. In our first study, a significant response following treatment initiation was not reached at 1 week but at 2 weeks, 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 days with Hépar, shorter than with controls (p=0.013). These results confirm that the consumption of 1L Hépar per day significantly

shortens mean time to obtain response to the treatment. Altogether, results from the first and the second study suggest in patients responding to treatment that the effect occurred grossly after one week. The use of e-diaries and stools photographs in this outpatient population contributed to more accurately show the effect of Hépar in 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. Part of, or all the patients likely had already tried Hépar to improve their symptoms of constipation. As a consequence, at least part of the patients may have been aware of the group they had been attributed to. This might have impacted the results we observed between the Hépar and placebo groups. Nevertheless, the way this effect occurred is not simple to determine (22).

A placebo effect can be easily imagined. The 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 and see a GP for their constipation most probably already tried Hépar and estimated that the consumption of this mineral water could not be sufficient for them. As a consequence, it may be hypothesized that part of the patients attributed to the Hépar group could have 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 patients of the placebo group 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 fibre 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 one century without any question regarding its safety, which clinical studies confirm. Efficacy and safety of 1L per day of Hépar support its use as a first-line treatment of functional constipation before considering drug therapy.

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References

1. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol. 2011;25(1):3-18.

2. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(9):1582-91; quiz 1, 92.

3. Zeitoun JD, de Parades V. [Chronic constipation in adults]. Presse Med. 2013;42(9 Pt 1):1176-85.

4. Maxion-Bergemann S, Thielecke F, Abel F, Bergemann R. Costs of irritable bowel syndrome in the UK and US. Pharmacoeconomics. 2006;24(1):21-37.

5. Wald A, Scarpignato C, Kamm MA, Mueller-Lissner S, Helfrich I, Schuijt C, et al. The burden of constipation on quality of life: results of a multinational survey. Aliment Pharmacol Ther. 2007;26(2):227-36.

6. Piche T, Dapoigny M, Bouteloup C, Chassagne P, Coffin B, Desfourneaux V, et al. [Recommendations for the clinical management and treatment of chronic constipation in adults]. Gastroenterol Clin Biol. 2007;31(2):125-35.

7. Dupont C, Campagne A, Constant F. Efficacy and safety of a magnesium sulfate-rich natural mineral water for patients with functional constipation. Clin Gastroenterol Hepatol. 2014;12(8):1280-7.

8. Rome Fundation. Rome III criteria 2006 [Available from: http://www.romecriteria.org/.

9. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920-4.

10. Bouchoucha M, Devroede G, Bon C, Bejou B, Mary F, Benamouzig R. Is-it possible to distinguish irritable bowel syndrome with constipation from functional constipation? Tech Coloproctol. 2017;21(2):125-32.

11. Bellini M, Gambaccini D, Usai-Satta P, De Bortoli N, Bertani L, Marchi S, et al. Irritable bowel syndrome and chronic constipation: Fact and fiction. World J Gastroenterol. 2015;21(40):11362-70.

12. Sanchez MI, Bercik P. Epidemiology and burden of chronic constipation. Can J Gastroenterol. 2011;25 Suppl B:11B-5B.

13. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J. 2012;24(3):69-71.

14. Esteban E, Rubin CH, McGeehin MA, Flanders WD, Baker MJ, Sinks TH. Evaluation of Infant Diarrhea Associated with Elevated Levels of Sulfate in Drinking Water: A Case-Control Investigation in South Dakota. Int J Occup Environ Health. 1997;3(3):171-6.

15. Gomes PB, Duarte MA, Melo Mdo C. Comparison of the effectiveness of polyethylene glycol 4000 without electrolytes and magnesium hydroxide in the treatment of chronic functional constipation in children. J Pediatr (Rio J). 2011;87(1):24-8.

16. Heizer WD, Sandler RS, Seal E, Jr., Murray SC, Busby MG, Schliebe BG, et al. Intestinal effects of sulfate in drinking water on normal human subjects. Dig Dis Sci. 1997;42(5):1055-61.

17. Murakami K, Sasaki S, Okubo H, Takahashi Y, Hosoi Y, Itabashi M. Association between dietary fiber, water and magnesium intake and functional constipation among young Japanese women. Eur J Clin Nutr. 2007;61(5):616-22.

18. Vu MK, Nouwens MA, Biemond I, Lamers CB, Masclee AA. The osmotic laxative magnesium sulphate activates the ileal brake. Aliment Pharmacol Ther. 2000;14(5):587-95.

19. WHO. Sulfate in drinking water. Background document for development of WHO Guidelines for Drinking-water Quality. WHO/SDE/WSH/0304/114. 2004.

20. Izzo AA, Gaginella TS, Mascolo N, Capasso F. Nitric oxide as a mediator of the laxative action of magnesium sulphate. Br J Pharmacol. 1994;113(1):228-32.

21. Ikarashi N, Ushiki T, Mochizuki T, Toda T, Kudo T, Baba K, et al. Effects of magnesium sulphate administration on aquaporin 3 in rat gastrointestinal tract. Biol Pharm Bull. 2011;34(2):238-42.

22. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. Nat Rev Gastroenterol Hepatol. 2015;12(8):472-85.

23. Rantis PC, Jr., Vernava AM, 3rd, Daniel GL, Longo WE. Chronic constipation--is the work-up worth the cost? Dis Colon Rectum. 1997;40(3):280-6.

24. Sonnenberg A, Koch TR. Physician visits in the United States for constipation: 1958 to 1986. Dig Dis Sci. 1989;34(4):606-11.

25. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. Aliment Pharmacol Ther. 2011;33(8):895-901.

26. SNFCP. [Recommendations for the clinical practice: Management of constipation] 2016 [Available from: http://www.snfcp.org/rc/org/snfcp/htm/Article/2011/20111201-151423-011/src/htm_fullText/fr/Constipation%20(RPC%20TC%202017).pdf

Figure Legends

Figure 1. Flow chart of the patients.

ITT: Intent-to-treat; PP: Per protocol; PP+: Modified per protocol

Figure 1

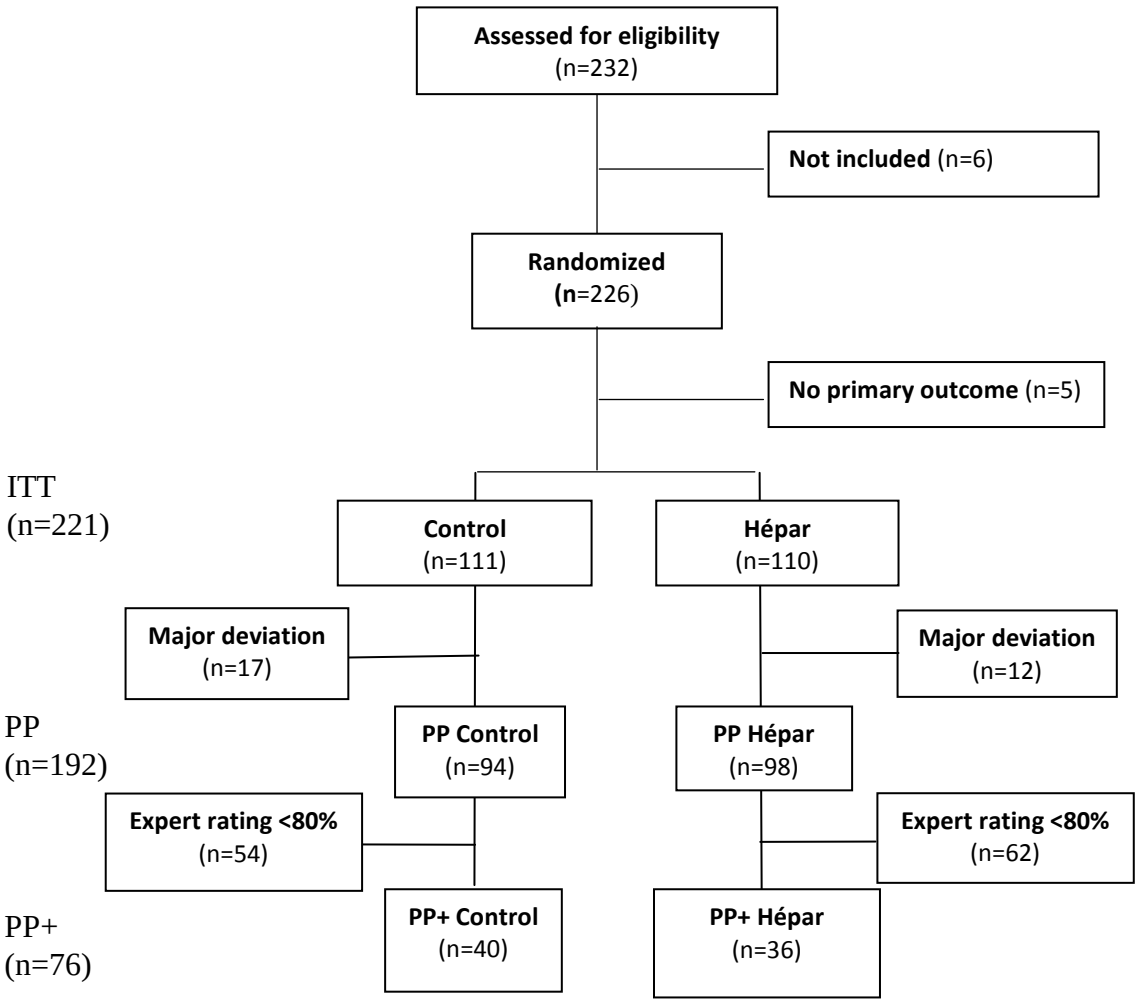
Assessed for eligibility
(n=232)
Not included (n=6)
Randomized
(n=226)
No primary outcome (n=5)
ITT
(n=221)
Control
(n=111)
Hépar
(n=110)
Major deviation
(n=17)
Major deviation
(n=12)
PP
(n=192)
PP Control
(n=94)
PP Hépar
(n=98)
Expert rating <80%
(n=54)
Expert rating <80%
(n=62)
PP+
(n=76)
PP+ Control
(n=40)
PP+ Hépar
(n=36)

Table 1. Rome III scoring according to the frequency of symptoms over the two weeks preceding measurement

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

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

	Control N=111	**Hépar** N=110	**Total** N=221
Age (years), mean ± SD	41.3 ± 10.6	41.4 ± 11.4	41.4 ± 10.9
Height (cm), mean ± SD	164.0 ± 7.0	163.7 ± 5.6	163.9 ± 6.3
Weight (kg), mean ± SD	66.0 ± 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 ± 5.0
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 (79.0)	172 (80.8)
Moderate, [23-34]	19 (17.6)	22 (21.0)	41 (19.2)
Severe, ≥35	0 (0.0)	0 (0.0)	0 (0.0)

BMI: Body mass index; ITT: Intent-to-treat; VAS: Visual analog scale

Table 3. Response to the 14-day treatment with a low-mineral water or 1L 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)	*0.001*	25 (26.6%)	42 (42.9%)	*0.018*	5 (12.5)	13 (36.1)	*0.016*
Stool frequency (n/day), 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 (34.0)	14 (20.9)		9 (42.9)	6 (26.1)	
Grade 3-5 (normal)	34 (65.4)	52 (72.2)		32 (64.0)	49 (73.1)		11 (52.4)	16 (69.6)	
Grade 6-7 (loose or liquid)	1 (1.9)	6 (8.3)		1 (2.0)	4 (6.0)		1 (4.8)	1 (4.3)	
Rome III Score, mean ± SD	12.3 ± 5.8	12.3 ± 6.0	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 D14 (Visit 2)	32.5 ± 27.1	21.2 ±22.0		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 ± 27.0	-11.3 ± 26.1	*0.002*	-2.5 ± 27.0	-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

*Repeated measures non-parametric analysis of covariance (ANCOVA)
ITT: Intent-to-treat; PP: Per protocol; PP+: Modified per protocol; VAS: Visual analog scale

Table 4. Difference between patient and expert stool scoring on the 7-grade Bristol scale: Difference = figure provided by the patient – figure provided by the expert. 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)

Table 5. Characteristics at inclusion and response to treatment at day 14 (Visit 2). Results are presented for patients providing photographs for lower or higher than 25% of their stools (ITT population)

	<25% N=17	**≥25%** N=202	**Total** N=219	***p***
Age (years), mean ± SD	38.6 ± 9.7	41.5 ± 11.0	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 ± 5.0	
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)	0 (0.0)	
Responder to the treatment, n (%)*	8 (47.1)	79 (39.1)	87 (39.7)	*0.520*
Stool frequency (n/day), mean ± SD*	0.9±0.6	0.8±0.4	0.8±0.5	*0.9158*

* At Visit 2

BMI: Body mass index; VAS: Visual analog scale