1. Introduction

Migraine is a disabling disorder with a life time prevalence of 13-33% (Launer et al., 1999). Several studies suggest that migraine can be considered as a complex neurogenic inflammatory disorder (Monteith and Goadsby, 2011; Waeber and Moskowitz, 2005; Wang et al., 2010), but the pathophysiology is still not fully understood (Samsam et al., 2010). Associations were found between migraine and gastrointestinal disorders including irritable bowel syndrome, inflammatory bowel disease and celiac disease (Van Hemert et al., 2014). These associations have been found in two directions: migraine patients have more often gastrointestinal disorders compared with healthy controls and patients with gastrointestinal disorders more often suffer from migraine compared to control groups. These associations could be explained by an increased intestinal permeability, which could be a cause or consequence of these gastrointestinal disorders (Duersken et al., 2005; Kerckhoffs et al., 2010; Piche et al., 2009; Salim and Soderholm, 2011). Increased intestinal permeability can allow leakage of undigested food particles and bacterial components like lipopolysaccharides into the bloodstream; the leaky gut hypothesis (Parlesak et al., 2000). These endotoxins can trigger a response provoking migraine (Covelli et al., 2003; Mennigen and Bruewer, 2009). Consequently, diminishing intestinal permeability may reduce the frequency and/or the intensity of migraine attacks.
Probiotics are living microorganisms which, when administered in adequate amounts, confer a health benefit to the host (FAO/WHO, 2001; Hill et al., 2014). Probiotics have been proven in vitro as well as in vivo to prevent damaging of the epithelial barrier (Ohland and Macnauthon, 2010). Furthermore, they are able to improve the epithelial barrier in several ways, depending on the used bacterial strain (Anderson et al., 2010; Miyachi et al., 2012). They can increase the mucus production of the goblet cells, they are able to stabilise the tight junctions between the epithelial cells and they can enhance IgA production (Ohland and Macnauthon, 2010). Probiotics can also have an indirect effect on the resident microbiota. For example, some probiotic bacterial strains directly kill pathogenic bacteria by secreting antimicrobial factors (Liévin et al., 2000). They can also compete with pathogens for binding sites on the epithelial cells (Neesser et al., 2000), which improves the barrier function.

So far, no clinical randomised controlled trials studying the influence of probiotics on migraine have been published. An uncontrolled study with a combination of various bacterial strains (Lactobacillus acidophilus DDS-1, Lactobacillus bulgaricus, Enterococcus faecium and Bifidobacterium bifidum, strain numbers for the latter were not indicated in the publication) and vitamins, minerals, micronutrients, and herbs in 40 migraine patients demonstrated that 60% of the migraine patients experienced almost total relief from migraine attacks (Senseng et al., 2001). It remains unknown if this improvement was due to placebo effects, one or more bacteria, or due to the other nutrients.

To study the possible association between migraine, intestinal permeability and probiotics and to assess therapeutic consequences, large scale clinical studies with probiotics in migraine patients are needed. We started with an open-label pilot study with a multispecies probiotic product to assess feasibility, possible adverse reactions, and a first impression of clinical efficacy in migraine patients.

## 2. Materials and methods

### Subjects

Participants were recruited via the recruitment database of Wageningen University, advertisements on the staff website of hospital ‘Gelderse Vallei’ in Ede, and by advertisements on notice boards at Wageningen University. Subjects willing to participate were screened by means of a medical screening questionnaire. Subjects fulfilling the International Headache Classification (ICHD-II) criteria, aged ≥ 18 years, and who had at least 4 migraine attacks per month with a stable pattern were eligible for the study. Exclusion criteria were chronic headache, medication-dependent headache, or other types of headaches, the use of antibiotics up to two months before the start of the study and the use of probiotics, other than used during this study during or up to two weeks before the start of the treatment period. All participants gave their written informed consent. The pilot study was approved by the Medical Ethical Committee of Wageningen University (dossier 11/44) and was performed according to the principles of the Declaration of Helsinki.

### Study design

Between February and June 2012 participants received 2 g of the multispecies probiotic product Ecologic® Barrier (Winclove Probiotics, Amsterdam, the Netherlands) daily for 12 weeks. The product (\(2.5 \times 10^9\) cfu/g) contains the following bacterial strains: Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcus lactis W19 and Lactococcus lactis W58. All these strains have been used before in different combinations in clinical trials showing a health benefit (Koning et al., 2008; Lamprecht et al., 2012; Niers et al., 2009; Persborn et al., 2013, Lamprecht, 2012). Compliance was measured every four weeks by counting the remaining sachets with probiotics.

Baseline number of migraine days per month were based on recall of the participants. At baseline and after 12 weeks of ingestion of the probiotics, the participants completed two headache questionnaires: The Migraine Disability Assessment Scale (MIDAS) and the Henry Ford Hospital Headache Disability Inventory (HDI), to assess intensity of the migraine (Jacobson et al., 1994; Stewart et al., 1999). The MIDAS questionnaire assesses missed days of activity, but also days in which the productivity was reduced by at least half during the last three months. The HDI questionnaire focussed on the functional and emotional feelings about having headaches.

During the study period, the participants completed a headache diary daily. In this diary, frequency and intensity (10-point Likert scale) of migraine attacks, used medication and gastrointestinal complaints were recorded. The diaries were handed out, discussed and collected every 4 weeks.

### Statistical analysis

We performed a sample size calculation based on previous drug trials aimed at reducing the number of days with migraine (Bensenor et al., 2001; Diener et al., 2004; Pfaffenrath et al., 2002). From these studies we derived the standard deviation (SD) of the effect to be within 1.3 and 2.1 days. Using these estimates of the SD in the formula \(n = 7.9 \times (SD/D)^2\) (D = the expected change between baseline and 12 weeks), it was calculated that for an effect of 1 days (reduction in migraine days/month) between 15 and 35 of patients were needed (using a confidence level of 5% and a power of 80%).
The difference of the mean number of migraine days between the four week periods and the difference of outcomes of the questionnaires were analysed using the paired samples t-test as these data were normally distributed. To compare the data of the migraine patients with bowel complaints with those of the migraine patients without bowel complaints, an independent samples t-test was used. IBM SPSS Statistics (version 19; Armonk, NY, USA) was used to analyse data. Data are given as mean±SD and P-values of <0.05 were considered as significant in all analyses.

3. Results

Baseline data

In total, 37 patients (3 males, 34 females) showed interest in participation in the study, of which 29 persons met the in- and exclusion criteria. From the initial 29 participants, 1 male and 26 females (mean age: 41.8±14.7 years; range: 20-64) completed the study. The other two 2 participants (1 male, 1 female) dropped out; one for unknown reasons and one because he/she did not like the taste of the probiotics. Mean duration of migraine was 19±14.2 years (range: 1-60 years); 7 of the 27 (26%) participants experienced auras during their migraine attacks. In 14 of the 26 (54%) female participants, menstrual periods were accompanied by migraine. Regular gastrointestinal complaints, such as obstipation and diarrhoea, were reported by 19 (70%) of the participants. Of all sachets with probiotics, 95% were returned empty. Over each period of 4 weeks, 52% of the participants took all sachets, 44% of the participants missed 1-5 of the 28 sachets and 4% missed more than 5 sachets. Four participants noticed constipation in the first two weeks of taking probiotics. This diminished in the third week after starting the intake of probiotics.

Migraine days

At baseline, the mean number of migraine days was 6.7±2.4 days per month. After 4 weeks of oral intake of probiotics, this was 6.3±2.3 days per month, which further decreased to 5.1±2.2 after 8 weeks and to 5.2±2.4 migraine days per month after 12 weeks. In comparison to the baseline measurement, the number of migraine days during the second (5-8 weeks) and third (9-12 weeks) period were significant lower (P=0.008 and P=0.001, respectively). At the end of the intervention period, the mean number of migraine days per month was decreased with 1.5 days (23%) compared to baseline (Figure 1, individual scores from +3 migraine days to -5 days). Of the 27 participants, 18 participants improved their number of migraine days after three months compared with baseline, 5 participants showed no difference, whereas the number of migraine days was increased in 4 patients. In patients with gastrointestinal complaints this decrease did not differ significantly from those without gastrointestinal complaints (P>0.05, data not shown).

Questionnaire outcomes

At baseline, the mean HDI score was 36.3±15.4 points. After 12 weeks of oral intake of probiotics, the HDI score decreased to 33.0±6.8 points (P=0.252). The mean MIDAS score decreased significantly from 24.8±25.5 points to 16.6±13.5 points (P=0.031).

Use of medication

Except for 4 participants, every participant used migraine specific medication. During the intervention period, the use of prophylaxes and triptans did not change. However, the use of over-the-counter analgesics (paracetamol, ibuprofen, aspirin) decreased from 333 dosages in weeks 1-4 to 221 in weeks 5-8 to 238 in weeks 8-12, a decrease of 29% (Table 1).
4. Discussion

In this open-label pilot study, the number of migraine days and migraine associated disability decreased significantly during 12 weeks treatment with a special designed probiotic mixture. Relevant adverse reactions did not occur and compliance was high. These findings suggest that further clinical studies with probiotics in migraine patients are feasible and warranted.

During our study, we saw a slight increase in the use of migraine specific medication, however, this increase was small and unlikely to be the cause of the decrease in migraine days we observed. The use of analgesics decreased by 29%, which is in the same range as the 23% decrease in migraine days we observed.

Not all participants experienced a beneficial effect of the probiotics. In our study, 67% of the participants showed a decrease in the number of migraine days, compared to 15% who showed an increase. This is in agreement with other probiotic studies, were often responders and non-responders are found (Reid et al., 2010). For instance, responder rates for irritable bowel syndrome are 18-80% (Hungin et al., 2013).

The study does not prove that the probiotic itself decreases migraine because a placebo effect cannot be excluded. However, the fact that the decrease of migraine days occurred not earlier than the second treatment period (5-8 weeks) and that this decrease continued the last treatment period (9-12 weeks) suggests that the improvement is not due to placebo effects. In placebo studies, improvement during placebo usually starts soon after treatment and diminishes after some weeks of treatment (Wang et al., 2012). A meta-analysis of migraine prophylaxis studies showed that the placebo-effect (percentage of patients showing a 50% improvement) was 22% while in our study this was at most 4/27=15% (Macedo et al., 2008). Placebo effects are highly dependent on the expectation of the participants (Elsenbruch et al., 2012), and we assume that participants expect stronger effects when they are participating in a drug trial than in a trial with a food supplement (de Groot et al., 2011). The lack of difference in probiotic treatment effect between migraineurs with and without gastrointestinal complaints, found in our study, suggests that the presence of gastrointestinal complaints is not a reliable selection criterion for effective treatment with a probiotic. A better selection criterion would be the presence of increased intestinal permeability. This can be demonstrated with different tests, like the lactulose/ mannitol test, or the use of radiisotope scanning tests (Scaldaferri et al., 2012). Increased intestinal permeability will be a selection criteria in our further studies.

Antihypertensive and antiepileptic drugs are well known migraine prophylaxes. They decrease migraine days with 21 to 62% (Bussone et al., 2005; Gales et al., 2010; Holroyd et al., 1991; Schellenberg et al., 2008; Shuhendler et al., 2009). In our study, migraine days decreased with 23%, which is within this interval. An advantage of probiotics is the lack of severe side effects. In our study the well-known and relatively mild side effects including bloating, diarrhoea, constipation and nausea (D’Souza et al., 2002; Hoveyda et al., 2009), disappeared within three weeks of treatment.

The strength of this pilot study is that it is the first study using probiotics in migraine patients. However, it had several limitations. Next to the lack of a placebo, we did not measure intestinal permeability at inclusion and after the intervention period. Furthermore, the type of migraine was not classified in detail and no run-in period was conducted. The number of migraine days at baseline were based on the recall of migraine attacks per month. Therefore, these indications may not be as reliable as it could be with a run-in period. However, the number of migraine days at baseline was comparable with the number of migraine days during the first four weeks of intervention which suggests that baseline data were reliable. The use of analgesics decreased during the study. However, no baseline measurement of the medication use was gathered, so these data could not be compared with the use of medication before the intervention period.

Nevertheless it can be concluded that probiotics may have a positive influence on the severity and frequency of migraine and that large scale clinical randomised placebo-controlled studies are warranted to evaluate working mechanisms and clinical efficacy. The probiotic food supplement used in this study may decrease migraine, both in frequency and intensity. This finding supports the leaky gut hypothesis. Feasibility and lack of adverse reactions justify further placebo-controlled studies.
The effects of probiotics on migraine – a pilot study

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Conflicts of interest

SwH is employee of Winclow b.v., producer of probiotic food supplements. The other authors report no conflicts of interests.

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