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Does Preprandial Oral Lactase Supplement Reduce Abdominal Pain in Lactose-intolerant Adult Patients after a Lactose-containing Meal?

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Does preprandial oral lactase supplement reduce abdominal pain in lactose-intolerant adult patients after a lactose-containing meal?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not preprandial oral lactase supplement reduces abdominal pain in lactose-intolerant adult patients after a lactose-containing meal.

STUDY DESIGN: A systematic review of three randomized, blinded, controlled primary research studies published between the years of 2010 and 2018.

DATA SOURCES: One randomized controlled trial (RCT), one randomized comparative study, and one randomized crossover study evaluating the efficacy of 9,000 units of preprandial oral lactase supplement in reducing abdominal pain due to lactose intolerance (LI). All studies were published in peer-reviewed journals and found via the use of PubMed, Elsevier, and OVID. The particular articles were selected based on their novelty and relevance to the clinical question.

OUTCOMES MEASURED: LI patients used a visual analogue scale questionnaire and maintained a diary to report the severity of their symptoms, tolerability, and adverse events. Clinical investigators evaluated compliance and calculated a symptom score.

RESULTS: Ojetti et al. reported a large reduction in abdominal pain in the tilactase group comparing to the placebo group. De Vrese et al. found no significant reduction in abdominal pain with *Aspergillus oryzae* lactase treatment. Francesconi et al. proved an experimental Perlatte® to be non-inferior to a commercially available Lactaid®, however, the difference between the two products was not statistically significant.

CONCLUSIONS: The evidence presented in this review is conflicting as to whether or not preprandial oral lactase supplement reduces abdominal pain in LI adult patients after a lactose-containing meal. The future research should consider genetic testing of the participants and distinguishing subjective lactose intolerance symptoms from a true lactase deficiency.

KEY WORDS: lactose intolerance, lactose malabsorption, hypolactasia, and lactase supplement

INTRODUCTION

Lactose intolerance (LI) is a clinical syndrome of lactase deficiency with the most frequent complaint being abdominal pain, followed by: diarrhea, flatulence, bloating, headache, fatigue, and muscle or joint pain. In the United States, the prevalence of LI is estimated to be 15% among Caucasians, 80% among African Americans, and up to 53% in the Hispanic population.[1,2] Being one of the most common genetic diseases in the Western world,[3] LI requires dietary restriction and careful meal planning by those who are affected, and it may negatively affect the quality of life for such individuals.

An exact number for the annual cost of LI has yet to be determined. A proper evaluation of LI comprises of a primary care visit, a gastroenterologist visit, a hydrogen breath test, a blood glucose or a stool acidity tests, and a nutritionist's consultation at a minimum. A dairy-free diet, as well as calcium and vitamin D fortified products, come at an additional cost. The available over-the-counter Lactaid supplement currently retails at approximately $0.25/caplet, while calcium and vitamin D supplements approximately cost $0.10/tablet.[4] Furthermore, LI-associated hypocalcemia and low vitamin D intake leads to an increased public health burden from fractures, osteoporosis, and rickets in children.[1,2,5-7] According to the recent report by the Health Care Cost Institute, between the years of 2012 and 2016, there has been a 129% increase in physician assistant (PA) and nurse practitioner (NP) primary care visits.[8] This places PAs at the front line of recognizing and treating LI in a primary care setting, as well as providing gastroenterology referrals.

LI results from a deficiency of a brush border enzyme responsible for lactose hydrolysis to glucose and galactose in the small intestine. When intestinal lactase level is low, lactose catabolism is disrupted. As such, lactose remains in the bowel lumen and draws water due to

osmotic force, which ultimately results in gastrointestinal (GI) symptoms. The four main types of LI include: primary LI (absent or reduced lactase activity from birth known as galactosemia), secondary LI (due to digestive tract inflammation), late onset lactase deficiency (decrease in lactase with aging), and temporary lactose malabsorption in newborns (physiological).[1,2]

Because LI can manifest itself at any age and is diet-dependent, this condition is often underreported and the diagnosis is often delayed or attributed to other conditions such as irritable bowel syndrome (IBS) or gastroesophageal reflux. Once recognized, LI requires individualized treatment because it depends on the person's genetic expression of the lactase gene, GI bacterial flora and motility, as well as the individual's perception of the symptom severity and its interference with daily activities. In addition, there is a wide spectrum of the doses of ingested lactose needed to produce symptoms in patients, which makes it difficult to develop a universal approach to LI treatment. The primary existing method of treatment is implementation of dairy-free and low fermentable oligo-, di-, monosaccharides and polyols (FODMAP) diets. However, such an approach of avoiding lactose-containing foods is restrictive, cost-ineffective, and carries a certain health risk for LI patients, as described in the previous paragraphs.

A promising and seemingly cost-effective treatment method evaluated in this review is the oral exogenous lactase supplement. For instance, Lactaid® is currently recognized as "safe for human consumption"[9] by the Food and Drug Administration (FDA), however, it has not yet been approved for medical use in the United States. If the exogenous lactase supplement is indeed proven to be effective for GI symptoms reduction, specifically abdominal pain, it could minimize vitamin D and calcium-associated deficiencies in the LI population and decrease overall public health burden.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not preprandial oral lactase supplement reduces abdominal pain in lactose-intolerant adult patients after a lactose-containing meal.

METHODS

The review included two randomized placebo-controlled clinical trials and one randomized comparative non-inferiority study published between the years of 2010 and 2018. The literature search was conducted using the following keywords: “lactose intolerance”, “lactose malabsorption”, “hypolactasia”, and “lactase supplement” in PubMed, Elsevier, and OVID databases. The search solely included randomized, blinded, controlled clinical trials published within 10 years. Excluded were the studies released over ten years ago, non-randomized studies, and studies that included products unavailable in the U.S. All articles were published in peer-reviewed journals in English. Francesconi et al. was co-published in Portuguese. The articles were selected based on their novelty and relevance to the clinical question. The selected studies utilized mean change from baseline, standard deviation (SD), P value, chi-squared test (X^2), relative risk reduction (RRR), absolute risk reduction (ARR), and number-needed-to-treat (NNT) to report the statistics. All study participants were older than 18 years of age who considered themselves lactose malabsorbers or with an existing diagnosis of primary hypolactasia, have not had a recent surgery or colonoscopy, and without a known GI comorbidities and substance abuse. Table 1 on the next page depicts the specific demographics and characteristics of each study.

To simulate lactose malabsorption, the experimental group in each study ingested preprandial lactase, while the control group received a visually identical placebo or reference product. Specifically, Ojetti et al.[6] administered 9,000 U of tilactase to their study participants,

followed by 25 g of lactose after 15 minutes. De Vrese et al.[7] patients ingested 9,000 FCC of *Aspergillus oryzae*-derived lactase together with 12.5 g of lactose. Both Ojetti et al. and De Vrese et al. administered visually identical placebo to their control groups.[6,7] Francesconi et al. administered 9,000 FCC of oral lactase (Perlatte®) to the experimental group and 9,000 FCC of Lactaid® to the control group and stated that all of the participants had "a major meal" after lactase ingestion.[5] In all three studies, the measured outcomes were reduction of incidence and severity of abdominal pain in LI patients. The severity of patient symptoms, tolerability of treatment, and the occurrence of adverse events were recorded via the Visual Analogue Scale (VAS). In addition, patients either noted their LI symptoms in a diary, or they were evaluated in-person, or both. Finally, investigators evaluated patient compliance and calculated a total symptom score. All three studies were approved by the local ethics research committees.

OUTCOMES MEASURED

The outcome measured was reduction of incidence and severity of abdominal pain after oral administration of lactase to LI patients before meals. In both the Ojetti et al. and Francesconi et al. studies,[5,6] patients recorded their GI symptoms in a diary. Symptoms were then assessed by VAS from 0-10 with 0 being "absent" and 10 being "severe" symptoms. For each patient, a score was calculated for abdominal pain. De Vrese et al. patients filled out a similar questionnaire where each symptom was evaluated on frequency, intensity, and duration and rated on a 0-6 scale with 0 being "no symptoms" and 6 being "unbearable" symptoms.[7]

RESULTS

All three of the studies compared adult patients of any gender or ethnicity in an experimental group receiving 9,000 units of preprandial lactase to a control group receiving a placebo (Ojetti et al. and De Vrese et al.) or a reference product Perlatte® (Francesconi et al.).

In addition, the multi-arm studies by Ojetti et al. and De Vrese et al. reported data from treatment with multiple doses of lactase and reference products,[6,7] however, for the purpose of this review, only data from 9,000 FCC lactase compared to a placebo experiments will be analyzed.

Table 1 - Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Intervention
Francesconi et al., 2016[5]	Randomized comparative non-inferiority study	128	18-60	Existing diagnosis of primary hypolactasia	History of smoking, colonoscopy or enema in the prior four weeks, GI comorbidities, lactase allergy	21	Administration of 9,000 FCC of oral exogenous lactase (Perlatte®) before breakfast, lunch, and dinner for 42 days
Ojetti et al., 2010[6]	RCT	60	18-65	Adults with GI symptoms after lactose ingestion and positive to the hydrogen lactose breath test	Age <18 or >65 years; diagnosis of small intestinal bacteria overgrowth; history of allergy to milk proteins	0	One-time administration of 4 pills of tilactase (9000 U) PO 15 min before the control lactose breath test, followed by 25 grams of lactose PO
De Vrese et al., 2015[7]	Randomized crossover study	30	> 18	Adults who consider themselves lactose maldigesters or with an existing diagnosis of lactose maldigestion	Participation in another clinical trial within 30 days, surgery within the last 3 months, known metabolic or GI disorder and/or medication for it, psychiatric disorder, or substance abuse	6	Ingestion of one capsule of 9000 FCC acid lactase from *Aspergillus oryzae* together with 150 ml of milk fortified with 5 g of lactose on five days separated by four periods of two-week wash-outs

Patients in all studies had to have an existing diagnosis of lactose maldigestion or a history of GI symptoms after lactose ingestion. Furthermore, they had to test positive to the hydrogen lactose breath test, which is a standardized quantitative measure of lactose malabsorption. History of substance abuse, milk protein allergy, GI comorbidity or recent intervention were universally considered as exclusion criteria due to non-specificity of GI symptoms and risk of impaired digestion and skewed data. A complete set of inclusion and exclusion criteria can be found in Table 1 above. In each study, the qualified subjects were required to undergo the lactose hydrogen breath test at every visit to ensure compliance with the interventions.

The Ojetti et al. study[6] was performed at a study center and lasted eight hours of one day. Sixty patients were randomized to three 20 patients-treatment groups: the tilactase group, the placebo group, and the *Lactobacillus reuteri* group. All patients in all groups completed the study. Refer to Table 2 below for a summary of results from this study. X^2 and Fisher's exact tests were used to determine incidence of abdominal pain. The treatment effect was reported as mean ± SD; the tilactase group experienced a change in symptom score from 8.05 ± 1.05 (baseline) to 2.00 ± 1.38 (after treatment), while the placebo group score changed from 7.90 ± 1.16 (baseline) to 7.10 ± 0.72 (after treatment). P value reported was less than 0.01. Such results were interpreted as a large reduction in pain for the patients.

Table 2 – Efficacy of 9,000 U tilactase in reduction of abdominal pain intensity (data from Ojetti et al.[6])

Study group		Mean ± SD	P value, CI
9,000 U tilactase	baseline	8.05 ± 1.05	< 0.01, not reported
	after treatment	2.00 ± 1.38	
Placebo	baseline	7.90 ± 1.16	
	after treatment	7.10 ± 0.72	

The De Vrese et al. study[7] consisted of five study center visits separated by four two-week periods. 30 subjects enrolled in the study and were randomly assigned to either a) 9,000 FCC lactase group, b) 3,300 FCC lactase group, c) placebo group, d) 10^9 *Streptococcus thermophilus* plus 10^9 *Lactobacillus delbrückii* ssp. *bulgaricus*, e) combination preparation of (b) and (d). 1 patient failed to follow up, and 5 patients were not proven to be lactose malabsorbers via the hydrogen breath test. A total of 24 patients were included in statistical analysis. As displayed in Table 3 below, Friedman test and multiple post hoc Wilcoxon comparisons without Bonferroni corrections showed the pain score as 0.4 ± 0.7 (mean ± SD) after 9,000 FCC lactase and 0.7 ± 0.9 after placebo treatment. Additionally, the authors report an average 45% of relative pain reduction with P value of 0.008. Such statistical values imply a significant statistical effect, however, considering that the majority of patients reported abdominal pain symptoms as few and mild in intensity (75th percentile score was 1.0 in the 9,000 FCC lactase group and 1.3 in the placebo group), the beneficial effect of 9,000 FCC lactase is not well-demonstrated in this study.

Table 3 – Effect of 9,000 FCC Lactase from *Aspergillus oryzae* on Abdominal Pain Strength (data from De Vrese et al.[7])

Study group	Median (25/75th percentile)	Mean ± SD	Relative % pain reduction	P value, CI
9,000 FCC lactase	0.0 (0.0/1.0)	0.4 ± 0.7	45%	0.008, not reported
Placebo	0.0 (0.0/1.3)	0.7 ± 0.9		

Francesconi et al.[5] evaluated the participants in four in-person visits to the study center on days 0, 14, 28, and 42. 129 persons were randomly assigned to an experimental product group (66 patients) and a reference product group (62 patients). Due to consent withdrawal, loss to follow-up, adverse effects, and protocol deviation, the experimental group consisted of 64 patients who received 9,000 FCC Perlatte®- Eurofarma Laboratorios S.A., and the reference group included 60 patients treated with 9,000 FCC Lactaid®- McNeilNutritionals, USA. Table 4

below summarizes the results from this study. 31% of patients receiving Perlatte®- experienced abdominal pain compared to 38% of patients in the reference product group. The NNT value in this study was 15, meaning that for every 15 patients with LI treated with preprandial Perlatte®, one more case of abdominal pain will be prevented compared to that of Lactaid®. The P value in this study, calculated by Fisher's exact test, was reported to be 0.453 with CI of [-31; -3.2] for abdominal pain. This means that, in fact, experimental treatment is not statistically different from the reference product.

Table 4 – Comparison of prevention of abdominal pain between Perlatte® and reference product (derived from Francesconi et al.[5])

Control event rate (CER)	Experiment event rate (EER)	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)	P value, CI
0.38	0.31	0.19	0.07	15	0.453, [-31; -3.2]

DISCUSSION

In the U.S., Lactaid (Lactaid, Pleasantville, NJ), Lactodigest (Thompson Medical Company, New York, NY), and DairyEase (Glenbrook Laboratories, New York, NY) are widely available over-the-counter in drugstores. These supplements contain beta-galactosidase enzyme derived from bacteria or yeast. The FDA generally recognizes these products as "safe for human consumption," however, they have not been evaluated for medical treatment of GI symptoms caused by lactase deficiency. The generic lactase supplements are also available on the market; however, insurance plans require a prescription for coverage of any medication. Moreover, the degree of cost reimbursement largely varies by insurance provider.

Numerous studies have proven efficacy of the preprandial lactase supplement in improving the hydrogen lactose breath test results in LI patients as a quantitative marker of LI.

However, it has been unclear whether exogenous lactase is indeed an effective treatment for LI symptoms such as abdominal pain, nausea, diarrhea, flatulence, and bloating.

Among the three studies analyzed in this review, the Ojetti et al. study[6] conducted in Italy demonstrated the most significant reduction in incidence and severity of abdominal pain, proving preprandial ingestion of 9,000 U tilactase effective versus placebo. Tilactase also significantly reduced diarrhea, bloating, and flatulence. The authors also tested *Lactobacillus reuteri* as a novel approach to LI treatment, but tilactase produced the strongest effect with respect to *L. reuteri* and placebo. It is noteworthy that the subjects in this study were predominantly female, and that a thorough demographic profile description was lacking.

The De Vrese et al. study[7] reported a relative reduction in abdominal pain from the baseline, however, the individual scores of intestinal complaints did not exceed 1 or 2 on a 0-6 scale with both 9,000 FCC lactase from *Aspergillus oryzae* and placebo. Because the study was conducted in Germany, where the research ethics rules differ from those in the U.S., the administered dose of lactose before the hydrogen breath test constituted 12.5 g instead of the U.S. standard of 25 g. Nonetheless, 9,000 FCC lactase had the strongest effect on reducing flatulence and not abdominal pain, while abdominal pain was most relieved with a combination preparation of 3,300 FCC lactase and 10^9 *S. thermophilus* plus 10^9 *L. delbrückii* ssp. *bulgaricus*.

Francesconi et al.[5] revealed the new product Perlatte® to be non-inferior to Lactaid® in reducing abdominal pain; yet, the study did not include a placebo group. The authors justified the non-inclusion of the placebo group with the statement that Lactaid was known to improve the hydrogen breath test results of LI patients. However, Lactaid has not been universally proven to reduce abdominal pain or any other GI symptoms from which LI patients suffer. Therefore, Perlatte® effectiveness for abdominal pain cannot be concluded. It is also important to note that

the study was conducted in Brazil and that the administered dose of lactose prior to the hydrogen breath test was 50 g, exceeding the U.S. standard. The authors further reported a conflict of interest, as the study was sponsored by the manufacturer.

The other important limitation of all three studies, as well as of the search strategy used in this systematic review, is a lack of clear differentiation between lactase deficiency and lactose malabsorption. For instance, Ojetti et al. did not differentiate between LI patients and lactose malabsorbers.[6] Lactase deficiency signifies a reduced brush border enzyme activity. Lactose malabsorption is determined through the lactose hydrogen breath test. While the two aforementioned conditions can be objectively quantified, lactose intolerance comprises a syndrome of non-specific GI symptoms and lacks objective verification. Subsequently, because abdominal pain cannot be objectively measured, in all three studies it was self-reported via VAS, thus leaving room for subjective bias.

CONCLUSIONS

The reviewed studies demonstrated conflicting evidence as to whether preprandial oral lactase supplement reduces abdominal pain in LI adult patients after a lactose-containing meal. The Ojetti et al. study achieved a marked reduction in abdominal pain after tilactase treatment,[6] while De Vrese et al. reported “relevant” reduction in abdominal pain but not significant.[7] The Francesconi et al. study proved the new product Perlatte® to be non-inferior to Lactaid and demonstrated its potential in treating LI.[5]

The majority of published RCTs on LI concentrate on decreasing lactose in the hydrogen breath test, however, few studies focus on patient symptoms. None of the latter are known to have been conducted and published in the United States. Future research would benefit from the following two interventions. First, a thorough demographic profile of the participants should

include ethnicity and genetic analysis. Due to the diversity of the U.S. population, this may be a key intervention, although the cost and availability of such concomitant genetic testing in the U.S. may present difficulties for the research. Second, the study participants should have an established diagnosis of lactose malabsorption or lactase deficiency. While there is an overlap between the two conditions, and indeed both patient groups may present with LI symptoms, not all lactose malabsorbers qualify for lactase deficiency diagnosis.

Overall, exogenous lactase seems to be a promising therapy and potential first-line treatment for LI, which could replace dietary restriction and improve the quality of life of patients with intolerance to lactose.

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