A novel combination of alpha-lactalbumin and iron for the management of iron-deficiency anemia in women with menometrorrhagia: a pilot study

M. Angelucci

Department of Gynecology, Casa di Cura Santa Famiglia, Rome, Italy

ABSTRACT — OBJECTIVE: *Menometrorrhagia is an excessive and prolonged uterine bleeding occurring at irregular intervals and represents a common gynecological condition in perimenopausal women. Menometrorrhagia can be caused by submucosal myomas and endometrial polyps, although may be associated with hormonal disorders. Iron-deficiency anaemia, is a very prevalent conditions in this pathology. The aim of this study was to evaluate the effects obtained administrating iron and alpha-lactalbumin (α-LA) in perimenopausal women affected by functional menometrorrhagia and iron-deficiency anemia.*

PATIENTS AND METHODS: *To address this issue, a cohort of 12 perimenopausal women aged 45-53 years, who presented functional menometrorrhagia, was scheduled for surgery (hysterectomy or myomectomy), since unresponsive or non-compliant to hemostatic treatment with tranexamic acid or to hormonal therapy with norethisterone. Participants were divided into two groups, one consisting of women treated with tranexamic acid and the other with norethisterone. Both groups were treated with an oral association of 30 mg micronized dispersible ferric pyrophosphate (MDFP) and 300 mg α-LA, one tablet per day, for 3 months. Hemoglobin (Hb) was monitored as primary outcome and the detection of any side effects such as constipation, diarrhea, nausea, abdominal cramps, vomiting as secondary outcome.*

RESULTS: *After 3 months of treatment (T1) with MDFP and α-LA, Hb was significantly improved respect to baseline (T0). A higher increase of the Hb values was observed in the patients under hormone therapy, compared with the hemostatic approach, with an increase of 2.30 g/dl vs. 1.60 g/dl from baseline, respectively. No woman showed side effects.*

CONCLUSIONS: *Combined administration of MDFP and α-LA effectively restored the physiological iron status in perimenopausal women with functional menometrorrhagia, without the occurrence of side effects.*

KEYWORDS
Iron-deficiency anemia, Alpha-lactalbumin, Iron, Micronized dispersible ferric pyrophosphate, Menometrorrhagia.

INTRODUCTION

Menometrorrhagia, an irregular and heavy uterine bleeding, is a pathological condition that affects about 12% of the female population and becomes even more frequently in the perimenopause, with an incidence peak of 24%[1]. Once ruled out cancer and any obstetric origin, such as an ongoing pregnancy, menometrorrhagia can be either organic (caused by e.g. leiomyomas or endometrial polyps) or functional (caused by a hormonal imbalance, without visible alterations of the uterine structure)[2].

Corresponding Author

Michela Angelucci, MD; e-mail: michela.angelucci81@gmail.com

Available treatments include hemostatic and hormonal therapies[3]. They essentially aim to prevent the abnormal bleeding, reducing the occurrence of anemic states that may severely impact the patients' quality of life[4]. However, several women are unresponsive to these treatments, especially in the presence of functional menometrorrhagia, or fail to be compliant. In such cases, surgery (hysterectomy or myomectomy) represents the approach of choice.

Whether patients receive the pharmacological therapy or are scheduled for surgery, replenished iron stores are necessary to restore adequate hemoglobin (Hb) levels[5]. While an iron-enriched diet proved substantially ineffective in reverting deficiency states, both intravenous and oral iron represent viable treatments for iron deficiency anemia. However, the former requires patient hospitalization and raises concerns about possible harmful effects from repeated treatments[6]; the latter ensures better compliance, but often presents with severe gastrointestinal side effects, including constipation, diarrhea, nausea, abdominal cramps and vomiting[7]. These compliance issues are mainly encountered in patients who experience iron-related gastrointestinal intolerability and are often caused by high doses of iron not absorbed by intestine. This is a limitation of iron supplement therapy. Promoting iron absorption by alpha-lactalbumin (α-LA) and choosing the right type of iron to administer may limit the occurrence of side effects.

α-LA is a whey protein that constitutes approximately 22% of total protein and 36% of the whey proteins in human milk[8]. α-LA is able to increase mineral absorption such as iron. Data reported how peptides released during α-LA digestion have a high affinity for iron and can promote iron uptake by human intestinal Caco-2 cells[9].

In a study conducted by Laganà et al[10], preparations of micronized dispersible ferric pyrophosphate (MDFP) and α-LA opened a new scenario: this type of micro-coated iron proved to be better tolerated because of increased intestinal transport and bioavailability. Indeed, combined administration of MDFP and α-LA effectively restored the physiological iron status in pregnant women presenting with iron-deficiency anemia, without the occurrence of significant side effects[11].

Starting from these promising results, the aim of our study was to evaluate the effects of administration of MDFP associated with α-LA in perimenopausal women affected by functional menometrorrhagia with iron-deficiency anemia.

PATIENTS AND METHODS

This pilot prospective non-controlled study included a cohort of 12 perimenopausal women aged 45-53 years, who presented with functional menometrorrhagia due to fibromyalgia or adenomyosis. The study was conducted at the Department of Gynecology, Casa di Cura Santa Famiglia in Rome, Italy, following the Ethical principles of the Declaration of Helsinki and the national laws. All participants gave their oral informed consent. Inclusion criteria included: age >40 years; hemoglobin values (from Complete Blood Count) below 11 g/dl; patients scheduled for hysterectomy or myomectomy since unresponsive or non-compliant to hemostatic treatment with tranexamic acid or to hormonal therapy with progestogens. Women presenting with organic menometrorrhagia and those undergoing any other kind of pharmacologic/nutraceutical treatments were excluded from this study. Furthermore, women with other pathologies such as intestinal malabsorption syndrome were not included.

The 12 patients, all under pharmacological treatment before enrollment, were divided in two groups as follows: one group (6 women) under treatment with sublingual tranexamic acid, administered every 8 hours for 5 days, at the beginning of every bleeding episode; the other group (6 women) under treatment with oral norethisterone (10 mg- Bayer, Leverkusen, Germany), one tablet per day for 10 days, at the beginning of every bleeding episode. All patients continued the pharmacological treatment during the entire course of the study. At enrollment (T0), both groups also started treatment with an oral supplement containing iron and α-LA (30 mg MDFP + 300 mg α-LA – Emogut® Forte, Farmares Srl, Rome, Italy), one tablet per day for 3 months.

Hb (g/dl) was monitored as primary outcome and the occurrence of side effects such as constipation, diarrhea, nausea, abdominal cramps, vomiting as secondary. Baseline characteristics of the patients were collected at enrollment (T0). After 3 months of treatment (T1), the Total Blood Count test was repeated to measure the values of Hb and to evaluate the changes over time. At the end of the study, patients were asked for the occurrence of side effects such as constipation, diarrhea, nausea, abdominal cramps, vomiting.

STATISTICAL ANALYSIS

Statistical analysis was performed using Wilcoxon signed rank sum test for comparing two independent groups. The Mann Whitney test was used to compare the results of sensory processing evaluation among the groups. Mann Whitney categorical variables were expressed as percentages 50th percentile. A p-value < 0.05 was considered statistically significant.

RESULTS

Based on the inclusion and exclusion criteria, 12 women were enrolled in the study; their baseline features are summarized in Table 1. At the beginning of the study, all patients showed Hb levels below the lower limit. After 3 months (T1) of treatment with MDFP and

Table I. Average baseline characteristics of the patients included in the study. Data are expressed as means and standard deviations.

Characteristics of enrolled patients at baseline	Age (years)	Parity		Hemoglobin (g/dl)	Pathology	
		natural births	caesarean births		Fibromatosis (N)	Adenomyosis (N)
Tranexamic acid group (N=6)	50.5 ± 2.88	2 ± 1	1.5 ± 0.7	10.08 ± 0.62	4	2
Norethisterone group (N=6)	49.83 ± 3.43	1.67 ± 0.58	1.33 ± 0.58	9.97 ± 0.26	3	3

α-LA associated either with hormonal or hemostatic therapy, we observed a significant increase of Hb compared with T0 for both treatments (10.02 g/dl at T0 *vs.* 11.96 g/dl at T1, $p = 0.0313$) (Figure 1).

We further stratified the results by sub-dividing the patients in two groups, according to the elected therapy, and we found out that association of MDFP and α-LA led to a higher increase of the Hb values in the patients under hormone therapy, compared with the hemostatic treatment (12.30 g/dl *vs.* 11.50 g/dl) with an increase of 2.3 g/dl and 1.6 g/dl from baseline, respectively.

No significant difference between the groups neither for parity nor pathology was evidenced. Moreover, none of women who assumed iron and α-LA for 3 months showed any side effect throughout the whole study period (Table 2).

DISCUSSION

Menometrorrhagia is one of the most common gynecological conditions in perimenopausal women, and it can be associated both with hormonal imbalances and also with pathologies such as endometriosis, uterine fibroids and, more rarely, gynecological tumors. Several options are available for the treatment of menomet-

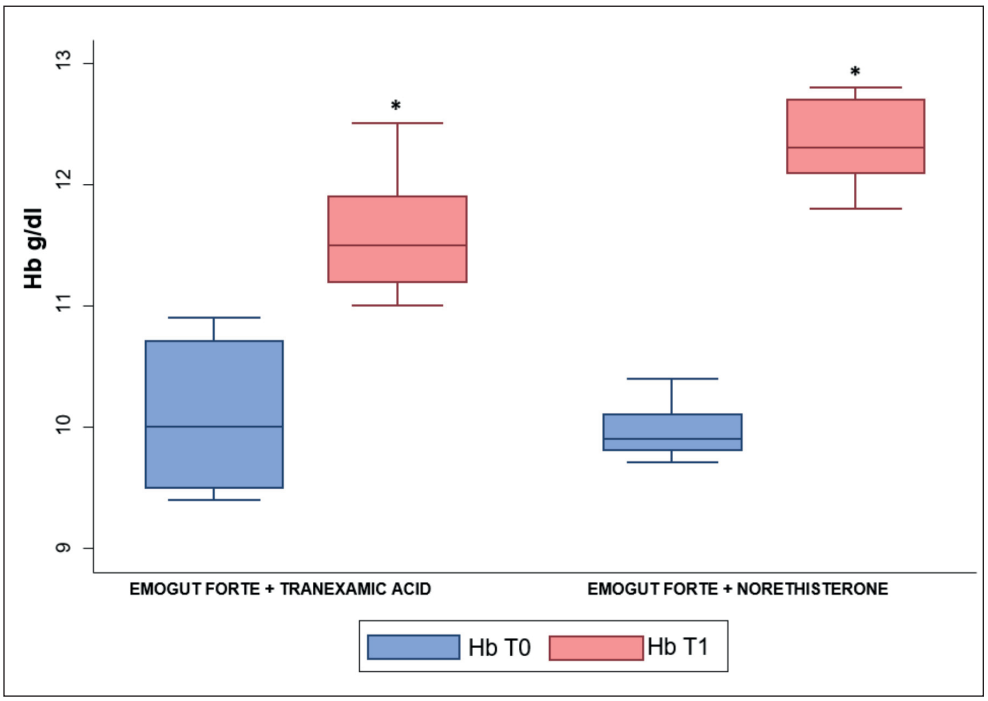

Figure 1. Differences between the two treatments after 3 months of therapy. A *p-value <0.05 was considered statistically significant. Statistical analyses were performed throughout Wilcoxon signed rank sum test.

Table II. Evaluation of the side-effects at the end of the study, after administration of MDFP and α-LA.

Patients	Side effects after administration of MDFP and α-LA				
	constipation	diarrhea	nausea	abdominal cramps	vomiting
N=12	–	–	–	–	–

rorrhagia. These include coagulation agents such as tranexamic acid, and hormone therapy.

Tranexamic acid can control bleeding acting as inhibitor of tissue plasminogen activator. Norethisterone may control uterine bleeding via a direct effect on endometrial blood vessels, it is a potent progestogen that binds progesterone receptor and produces changes in the endometrium.

Even though for many women bleeding management is achieved with these treatments, several patients are unresponsive. In this latter case, surgery (hysterectomy or myomectomy) represents the clinical option recommended. In patients scheduled for hysterectomy or myomectomy, iron deficiency and iron-deficiency anemia, are common conditions. Replenished iron stores are necessary to restore adequate Hb levels before going into surgery. Iron supplementation is the main strategy to control iron deficiency. Unluckily, most of the administration of iron may be associated with side effects like constipation, darkened stools, diarrhea, loss of appetite, nausea, stomach cramps, and vomiting. In this study the association of α-LA and MDFP effectively restored the physiological iron status in perimenopausal women with functional menometrorrhagia and iron-deficiency anemia, without the occurrence of side effects. Indeed, a significant increase in Hb levels was observed in all patients undergoing treatment, especially when administration of MDFP and α-LA was associated with progestogens.

These results are corroborated by the study conducted by Laganà et al[10], in which association of MDFP and α-LA showed a higher efficacy in improving parameters like Hb, ferritin, serum iron and hematocrit (Hct) and a safer profile than ferrous gluconate (FG), in pregnant women affected by iron-deficiency anemia.

This significant increase in Hb is probably due to the action of α-LA. α-LA is an important source of bioactive peptides and essential amino acids, including tryptophan, the direct precursor to serotonin and the neurosecretory hormone melatonin[12]. The biopeptides deriving from α-LA digestion have interesting biological actions[13] such as prebiotic, antimicrobial[14], anti-inflammatory[15], pro-apoptotic[16] and trophic action[17]. α-LA is also able to exert several physiological activities on gastrointestinal function and gut development, including motility and antimicrobial. What has also been seen is that α-LA is able to improve iron absorption. α-LA has two binding sites for calcium, one of which may be occupied by iron[18,19], and the peptides released during α-LA digestion are able to increase iron absorption significantly[9]. These peptides have a high content of negative charges, which may bind with divalent cations such as iron and form soluble complexes[18]. This prevents the formation of insoluble iron in the intestinal environment. Iron solubilization is the first step before iron is absorbed in the intestine, a greater iron solubility indicates more iron available for absorption[19]. Hegsted et al[20] suggested that glutamic acid may increase the absorption or deposition of iron. α-LA hydrolysate has a high content of glutamic acid and aspartic acid. These amino acids have more free carboxyl groups than other amino acids and can form iron complexes and enhance iron binding.

α-LA is also able to improve the intestinal absorption of some micronutrients, including iron, through the promotion of glucagon-like peptide-2 (GLP-2) secretion from gut endocrine cells[21]. GLP-2 has a trophic effect on the small intestine, stimulates the proliferation of intestinal crypts, increases membrane transporters in enterocytes and expands the surface area of the mucosal epithelium[22].

Unabsorbed iron in the intestine could promote the development of pathogenic enterobacteria that may use this available iron for virulence or colonization of the gastrointestinal tract[23]. Encouraging iron absorption by human intestinal cells, α-LA can make it less available to potential pathogens. In addition, the antibacterial peptides deriving from digestion of α-LA lead to a significant reduction of potentially pathogenic bacteria like S. Pneumoniae, Bacteroides, Clostridia, E. coli within intestinal microflora. On the other hand, thanks to its prebiotic action, α-LA promotes the growth of bacterial species such as lactobacilli and bifidobacteria that exert a beneficial action for the human body[24,25].

Also, unabsorbed iron promotes the increase of inflammatory pathways, such as neutrophil lipid peroxidation, NF-κB and proinflammatory cytokines activation, leading to intestinal inflammation[26]. Moreover, inflammation increases the iron regulatory hormone, hepcidin, that causes iron sequestration in the setting of inflammation[27]. In turn, α-LA shows beneficial anti-inflammatory and anti-nociceptive activity by inhibiting cyclooxygenase-2 (COX-2) and reducing the level of proinflammatory cytokines[28] and inflammatory mediators such as PGE2, IL-6, TNF-α, IL-β[29,30]. Therefore, the anti-inflammatory effect can be effective in improving iron availability and absorption.

Overall, the administration of α-LA, thanks to its various beneficial actions, combined with MDFP is able to restore adequate Hb levels without the occurrence of significant side effects, deriving from unabsorbed iron in non-responder women to hemostatic or hormonal therapy.

However, despite our interesting and promising results, there are a number of limitations due to the small cohort enrolled and the scarcity of other information. Larger and randomized studies are needed to standardize the use of α-LA as a valid support for preoperative martial therapy.

CONCLUSIONS

The combination of MDFP and α-LA efficiently increased Hb levels and promoted iron absorption in perimenopausal women with iron deficiency caused

by functional menometrorrhagia. The absence of side effects showed how the use of MDFP combined with α-LA assures the maximum of safety and tolerability.

Conflicts of interest:
The author reports no conflict of interest.

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