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Reduction of endometriosis-related pain: efficacy of trace elements in a double-blind, randomized, placebo-controlled trial

Endometriosis is a multifactorial, estrogen-dependent, inflammatory, gynecological condition that can result in long-lasting visceral pelvic pain dysmenorrhea, dyspareunia, noncyclical pelvic pain, and dyschezia and infertility which significantly impairs quality of life of women.[1] Today, therapeutic options for endometriosis are not enough to relieve pain in long-term. Some preliminary data suggest an effect of food supplement containing combination of metal trace elements (C2M2ZPSI or Nutri Endo), on the reduction of pain in women suffering from a revised American Fertility Society score (AFSr) stages I–IV endometriosis.[2] Our study aimed to evaluate the efficacy and safety of this combination of metal trace elements (Nutri Endo resulting from Nutripuncture [Nutrition Services Research Inc, Chicago, IL, USA] research or C2M2ZPSI) on the reduction of pain after 4 months of treatment as compared to placebo in patients with AFSr Stages II, III and IV endometriosis.

Our study was a randomized, double-blind, placebo-controlled, multicenter trial. Patients completed a placebo preinclusion period during a menstrual cycle (or 30 days for women with amenorrhea) to exclude placebo responders (at least 20% less pain). Patients were then randomized to receive C2M2ZPSI or a placebo for 120 days. Premenopausal women (18 to 45 years old) with a diagnosis of endometriosis (confirmed by laparoscopy and/or laparotomy) stage II-IV AFSr alone or associated with adenomyosis, with pain related to endometriosis ≥40 mm over visual analog scale (VAS) rated from 0 to 100 mm, were eligible. For patients previously treated stably (hormonal contraceptives, non-steroid anti-inflammatory drugs (NSAIDs), or any other modality) the period between treatment and inclusion had to be at least two months and 6 months for surgery. Women who were pregnant were excluded. Four visits between day -45 and day -30, day 0, day 60 and day 120 were planned. Patients assessed their pain daily on a 100 mm visual analog scale (VAS), and at each visit. The patients filled in the endometriosis health profile-30 (EHP-30) QoL questionnaire[3] (ranging from 0 [best health status] through to 100 [worst health status]) on day 0, day 60 and day 120. Urine pregnancy test was performed during each visit. Patients recorded their blood loss, use of NSAIDs and adverse events (AEs) and serious AEs (SAEs).

The primary endpoint was the difference in % of the area under the curve (AUC) mean for pain between day 0 and day 120 based on the daily recording of pain measured by the VAS from 0 to 100. Secondary endpoints were: 1) change in the total score of the EHP-30 questionnaire; 2) number of ibuprofen tablets consumed during the taking phase of the product; 3) percentage of days with blood loss and frequency of AE/SAE. A number of 23 patients per group was sufficient to detect a statistically significant difference of 20% on the percentage change in the AUC of pain (VAS) between the 2 groups (alpha risk of 5%; power of 90%), assuming a change of 10% in the placebo group and 30% in the C2M2ZPSI group and a common standard deviation of 20%. The number was increased to 60 patients to have 46 patients completing the study. The randomization was computerized, automated and centralized. The placebo and C2M2ZPSI tablets were similar (shape, size, color and appearance). The analysis (IBM-SPSS [IBM, Armonk, NY, USA] Statistics Version 21.0 software) included all randomized patients who took at least one dose of the product (intention to treat population). Patients undergoing surgery, a major therapeutic change and/or having developed a confirmed pregnancy or having stopped taking the drug during the study were excluded. The missing values were not replaced. The primary endpoint and secondary efficacy endpoints were compared using a Student's *t*-test.

A total of 63 women were randomized between May 28, 2015 and December 31, 2016 (32 C2M2ZPSI group and 31 placebo group) and 43 women completed the study (23 C2M2ZPSI group and 20 placebo group). The reasons for premature exit from the study were respectively in the C2M2ZPSI/placebo groups: withdrawal of consent (2/0); loss of follow-up (3/0); SAE (0/1); AE (0/4); pregnancy (0/1); other reasons (1/1); not specified (3/4). The characteristics of the patients at baseline are shown in Table I.

The average AUC for pain between day 0 and day 120 based on the daily recording of pain was significantly lower in the C2M2ZPSI group with an average AUC of 37 mm, compared to 64 mm in the placebo group ($P<0.001$). The mean change compared to the initial pain values, measured on day 30, day 60 and day 120 reached significantly lower values in the C2M2ZPSI group compared to placebo, with a reduction of 42 mm and 16.4 mm respectively ($P=0.001$) (Figure 1). The average number of ibuprofen tablets taken daily between day 0 and day 120 showed a lower trend in the

TABLE I.—*Demographic and clinical characteristics at baseline after the preinclusion period on placebo (ITT population).*

	Placebo N.=31	C2M2ZPSI N.=32
Age-mean (SD) years	3.4 (6.5)	35.7 (5.9)
Time since surgery, mean (SD) months	28.1 (28.5) *	37.8 (39,8)
Body mass index, mean (SD) kg/m^2	22.9 (3.3)	24.9 (7.1)
Duration of endometriosis, mean (SD) years	4.0 (3.3)	4.7 (4.9)
Intensity of pain (last cycle) - VAS 0-100	70.9 (16.0)	66.5 (14.1)
EHP score at day 0 - score 0-100	59.0 (14.6)	52.3 (24.8)
Psychological score HEP -score 0-100	18.2 (4.8)	13.3 (8.4)

EHP: endometriosis health profile-*30*, EHP-30 Pain (11 questions) control and powerlessness (6 questions), emotion (4 questions), social support (6 questions), self-image (3 questions); IIT: intention to treat; SD: standard deviation; VAS: visual analog scale.
*One missing data.

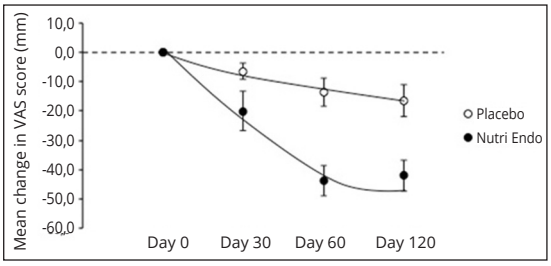

Figure 1.—Mean change of pain between day 0 and day 120. Values are expressed as mean±SD years.

C2M2ZPSI group (6.9; 7.7; 3.7 and 5 tablets / month) compared to placebo (13.7; 9; 11.6 and 10.1 tablets / month). The difference between the study groups was significant between day 60 and day 90 (P<0.01). There was no significant difference in the average percentage of the number of days with blood loss between day 0 and day 120. The EHP-30 score decreased between day 0 and day 120 from 58.96 to 50.71 in the placebo group and from 52.29 to 48.65 in the C2M2ZPSI group (P>0.05). Eighty-seven AEs were reported (42 in 18 patients (18/31 [58.1%] in the placebo group and 45 in 19 patients 19/32 [59.4%] in the C2M2ZPSI group) (P<0.05) No safety signal was detected.

In conclusion, and to our knowledge, this pilot study is a first of its kind. It showed that endometriosis-related pain was reduced by 66.1% and it impacted 91.3% of patients in the C2M2ZPSI group These encouraging results could be further investigated to understand if it acts on physiologic and/or histologic parameters.

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