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Efficacy of Evandol, a novel food supplement containing myrrh (MyrLIQ®), boswellia (BosLIQ®) and pineapple in reducing acute pain during intrauterine device insertion in nulliparous women. A pilot observational study

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SUMMARY: **Efficacy of Evandol, a novel food supplement containing myrrh (MyrLIQ®), boswellia (BosLIQ®) and pineapple in reducing acute pain during intrauterine device insertion in nulliparous women. A pilot observational study.**

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Aim. *To assess the efficacy of Evandol, a novel food supplement containing Boswellia (BosLiq®), myrrh (MyrLiq®), pineapple and seed oil from Buglossoides arvensis, in reducing the pain score during and post intrauterine device (IUD) insertion in nulliparous women.*

Method. *Patients that were to undergo IUD insertion were assigned to the treatment group and patients with the same baseline characteristics were assigned to the control group retrospectively. Patients in the treatment group took Evandol four days prior to IUD insertion and continued for three days post insertion. The control group patients did not receive Evandol therapy. Pain scores were recorded based on the Numerical Rating Scale (NRS) immediately after insertion and three days post insertion from both groups.*

Results. *There were significant differences between the control and the treatment group in terms of pain scores at the time of IUD insertion and at three days after insertion. The Evandol treated patients were primed four days before the insertion, leading to significant reduction of pain at the time of insertion. Evandol maintained its pain relief capacity even after three days as evidenced by significantly different pain scores for the control group.*

Conclusions. *Evandol, a unique herbal preparation, could help women overcome fear of pain during IUD insertion as evidenced by reduction in the pain score during insertion. Evandol seems to eliminate pain more efficiently compared to the control group after three days of post insertion. Further studies are needed to explore the temporal dynamics of pain relief in the days after insertion.*

What is new in this paper? *This study reports for the first time the beneficial effect of the novel herbal preparation Evandol as a possible acute pain relief solution for nulliparous women undergoing IUD insertion. Evandol could be administered in day clinics as an alternative to pharmacological preparations to overcome fear of pain without side effects.*

KEY WORDS: Food supplement - IUD - Pain control.

Introduction

Contraceptives are devices or methods for preventing pregnancy, either by preventing the fertilization of the female egg by the male sperm or by preventing implantation of the fertilized egg. Unintended pregnancy is expensive for both women and society in terms of medical costs, the costs of caring for more children and achieving personal/professional goals (1). Intrauterine devices (IUDs) are highly effective, safe and relatively inexpensive methods of contraception that may offer advantages for some women over other long-term methods, such as sterilization and Norplant (2). Different types of copper and levonorgestrel releasing (LNG-IUD) intrauterine

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devices are available on the Italian market. The most frequently used IUDs are the copper IUDs Nova-T 380 and Multi-safe 375, as well as two levonorgestrel-releasing IUDs (LNG-IUDs), one that releases 20 mcg of levonorgestrel per 24 hours (Mirena) and a low-dose device that releases 14 mcg per 24 hours (Jaydess).

Failure rates within the first year after insertion are 0.6% to 0.8% for the copper T 380 IUD, 0.2% for the 20-mcg LNG-IUD, and 0.9% for the 14-mcg LNG-IUD. In contrast to many forms of contraception, the effectiveness of IUDs is not heavily dependent on user compliance (3).

Fear of pain during insertion of an IUD may deter women from choosing the IUD as a method of contraception (4). Pain during insertion of an IUD can be associated with multiple causes including applying the tenaculum to the cervix to straighten the cervical canal, passing the uterine sound, inserting the IUD through the cervix, and myometrial contractions caused by the IUD irritating the uterine cavity. Pharmacological interventions for pain control during IUD insertion include analgesics, local anesthetics, and the use of prostaglandins to soften the cervix; however, there is wide variation in the use of these methods (5). Other non-pharmacological considerations such as pre-insertion counseling, the setting for the procedure, or the confidence of the provider may influence a women's level of anxiety, possibly affecting the patient's perception of pain and the overall experience (6).

The literature also revealed non-pharmacological interventions for pain relief with IUD insertion including delayed bladder emptying, aromatherapy, pre-placement counseling, and distraction during the procedure. Use of aromatherapy as a complementary treatment has been examined and shown to reduce anxiety associated with IUD insertion (7). Pre-placement counseling and distraction were also found to be effective at reducing anxiety (8). In a published study, Shahnazi and colleagues randomized 106 women to inhale ten drops of lavender scent or a placebo scent 30 minutes before IUD insertion. Pain scores after intervention did not show a significant difference between the lavender scent and the placebo groups. However, mean differences of anxiety in both groups was statistically significant, showing a positive effect of aromatherapy as complementary treatment. Further evaluation of additional interventions in managing IUD insertion-related pain is warranted.

Boswellic acids are the main bioactive constituents of frankincense, a traditional remedy of Indian, Chinese and African folk medicines, with antiarthritic, astringent, stimulant, expectorant and antiseptic properties. A bulk of experimental data from *in vitro* and *in vivo* studies, and pilot clinical trials support the potential of *Boswellia serrata* gum resin extract (BSE) for the treatment of various inflammatory diseases such as bowel disease, rheumatoid arthritis, osteoarthritis and asthma (9-15). Myrrh, a traditional natural medicine, is an aromatic gum resin, the plant stem resinous exudate of *Commiphora myrrha* (Nees) Engl. (Burseraceae) and various other species of the *Commiphora* family. It has many medicinal powers and has been used widely in clinic for treatment of pain and inflammatory diseases such as stomach complaints, skin infections, ache, dysmenorrhea, chest ailments and others, in India, China, Rome and Greece (16-18). Myrrh in particular was a common analgesic and was used for more than 2000 years to clean wounds and sores, until the Europeans discovered morphine. Pharmacological studies also have shown that myrrh possesses multiple activities including anti-inflammatory, cytotoxic, anesthetic and antimicrobial effects (19). *Ananas comosus* (pineapple) has long been used for medicinal purposes. Native cultures used it as a digestive aid and a remedy for skin disorders. Bromelain is a crude, aqueous extract derived from pineapple stems and fruits. In recent studies a wide range of therapeutic benefits have been suggested for bromelain, such as anti-inflammatory, anti-edematous, pain reducing, wound healing, anticoagulant, etc. (20, 21). *Buglossoides arvensis* (Ahiflower) oil is a dietary oil rich in stearidonic acid (20% SDA; 18:4 n-3). Additionally, Ahiflower oil contains gammalinolenic acid (GLA, 18:3 n-6) that also possesses anti-inflammatory properties associated with its conversion to its elongation product dihomo-gamma-linolenic acid (DGLA, 20:3 n-6) (22).

In this observational study, we evaluated the efficacy of the food supplement Evandol - a preparation that combines the beneficial properties of *Boswellia* (BosLiq®), myrrh (MyrLiq®), pineapple and Ahiflower - as a natural analgesic in a case-control group of nulliparous women undergoing IUD insertion. Evandol was provided as 0.68g capsules and each capsule was composed of 200mg of *Commiphora myrrha* fluid extract, 150mg of *Boswelia sacra Flueck* fluid extract, 80mg pineapple stem as source of bromelain and 70mg of *Buglossoides arvensis* oil.

Buglossoides arvensis oil (Ahiflower) is a dietary oil rich in the essential fatty acids, stearidonic acid (SDA) and gamma-linolenic acid (GLA). The myrrh furanodienes curzerene, furanoeudesma-1,3-diene and lindestrene are primarily responsible for the myrrh aroma as well as the analgesic properties of myrrh. MyrLIQ® is a *C. myrrha* liquid extract produced by Biosfered Srl (Academy spin-off of the University of Turin-Italy) and is characterized by a high content of bioactive furanodienes. BosLIQ® is a fluid extract of *B. sacra* produced by Biosfered Srl with a high content of bioactive constituents: AKBA (3-O-acetil-11-cheto-β-boswellic acid) and other boswellic acids. The resin gums were extracted with ethanol to obtain a liquid extract. The ethanol was then removed and the extract liquid concentrate was dissolved in food grade emulsifiers. Raw materials, intermediate and final products were analyzed using the latest technologies and strict quality control measures were performed during every stage of the production process.

Materials and methods

Study design

The present study was a pilot observational study of patients attending the gynecology outpatient clinic of Ferrara and Vicenza from January 2017 to April 2018.

Patients

Nulliparous women between 24 and 48 years old who were treated for IUD insertion were invited to participate in the study. The exclusion criteria were previous pregnancies, simultaneous use of oral or inhalatory corticosteroids, simultaneous use of acetylsalicylic acid (aspirin, cardioaspirin, Cardirene and Ascriptin at a dose range of 75-300mg/day), simultaneous use of other analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids) and use of estrogen and progesterone-based contraceptives. Patients were duly informed before enrollment about the purpose of the study and signed an informed consent related to the confidentiality of the personal data collected. The study was approved by a regional scientific committee. Patients who were enrolled in both the treatment group (n=38) and the control group (n=37) were similar in their sociodemographic and medical parameters.

Treatment

All the patients who were to undergo IUD insertion were provided with one 14-capsule pack of Evandol. Four days prior to IUD insertion, they were instructed to take one capsule in the morning and one in the evening. Immediately after IUD insertion, patients were asked to complete the Numerical Rating Scale (NRS) questionnaire to evaluate the pain experienced during insertion by circling the number between 0 and 10. Zero represented "no pain at all" whereas the upper limit represented "the worst pain ever possible." The patients were told to take Evandol at the same dose until they had finished all the capsules. The patients completed the NRS questionnaire three days after IUD insertion. The control group patients followed exactly the same timeline as the other treatment group without taking any Evandol capsules.

Data collected

The pain scores collected from patients at the time of IUD insertion were considered as T0 and three days post insertion as T3.

Statistical analysis

Demographic characteristics were analyzed by descriptive statistical techniques using mean, standard deviation and range. The Shapiro-Wilk test was used to show that the control and the treatment groups were not distributed normally. The differences in the pain scores between the control and the treatment group between T0 and T3 were analyzed using the Mann-Whitney test. The significance level was set at 0.05. Statistical calculations were performed using standard statistical software (Origin 9.0, OriginLab Co, Northampton, Massachusetts).

Results

A total of 75 patients (mean age of women was 30.1 years, ranging from 24 to 48 years) seeking IUD insertion participated in the study. The patients that were enrolled prospectively were assigned to the treatment group whereas the control group patients were matched retrospectively. At baseline, the groups did not significantly differ from each other with respect to their demographic characteristics as illustrated in Table 1. At T0, corresponding to the

time of IUD insertion, the mean pain scores among the control and treatment groups were 5.94±2.5 and 2.97± 0.97, respectively. Group pain score comparisons revealed that acute pain at the time of IUD insertion in patients treated with Evandol was significantly lower than in the untreated control group [P<0.05]. The analgesic properties of Evandol helped to reduce pain significantly even after three days of IUD insertion when compared with the control group. The results are summarized in Table 2.

Discussion

Women's perception of pain is multifactorial and likely to be influenced by cultural differences and personal experiences; IUD insertion-related pain is therefore difficult to predict. Nevertheless, factors associated with greater pain include nulliparity, not currently breastfeeding and longer time since last pregnancy; of these factors, nulliparity is the strongest predictor of pain (23). No comprehensive

TABLE 1 - PATIENT CHARACTERISTICS.

	Control	Evandol
N	37	38
Mean Age	29,5±3,1	30,5±4,8
Age range	24-36	24-48
Type of IUD inserted	Copper (n = 22) Jaydess (n = 11) Mirena (n = 4)*	Copper (n = 26) Jaydess (n = 10) Mirena (n = 2)

* *Patients complained of pelvic pain for 12/16 hours after insertion.*

TABLE 2 - COMPARISON OF PAIN SCORES AT T0 (TIME OF IUD INSERTION) AND T3 (3 DAYS POST-INSERTION).

T0									
Group	**N total**	**Mean**	**Standard Deviation**	**Normality Test (Shapiro-Wilk)**			**Mann-Whitney Test**		
				Statistic	**p-value**	**Decisione at level 5%**	**U**	**Z**	**Asymp. Prob>|U|**
Control	37	5,94595	2,5598	0,93723	0,03768	Reject normality	1168,5	5,01858	5,20556E-7
Evandol	38	2,97368	0,97223	0,885384	0,00101	Reject normality			
T3									
Group	**N total**	**Mean**	**Standard Deviation**	**Normality Test (Shapiro-Wilk)**			**Mann-Whitney Test**		
				Statistic	**p-value**	**Decisione at level 5%**	**U**	**Z**	**Asymp. Prob>|U|**
Control	37	2,21622	2,76018	0,77693	4,62485E-6	Reject normality	1009	3,77515	1,59908E-4
Evandol	38	0,21053	0,47408	0,49493	2,85154E-10	Reject normality			

strategy has been developed for managing pain associated with the insertion of IUD and no standard has been established. Current pharmacological strategies include: pre-insertion therapy (oral analgesia, cervical ripening/priming and local anesthesia), therapy given during the procedure (local anesthesia administered reactively) and post-procedure therapy (non-steroidal anti-inflammatory drugs [NSAIDs] and opioid analgesia). Non-pharmacological pain management strategies include psychological preparation and counselling before insertion and "verbal anesthesia" and distraction during the procedure (6). Evidence for non-pharmacological strategies for the management of pain during IUD insertion was limited. *Boswellia serrata* has been tested in human pain models for its analgesic activity both in-vitro and in preclinical studies. It significantly increased pain threshold and tolerance when compared to baseline and placebo with good safety and tolerability (24). A pilot study on bioactive constituents and analgesic effects of *Commiphora myrrha* extract has confirmed the analgesic properties in various pain-causing pathologies (25). However, there are no effective herbal mixtures which take into account the analgesic properties of single ingredients in alleviating acute pain during intrauterine device insertion. In this pilot study, we introduce for the first time Evandol, a patented herbal mixture which combines the pain killer qualities of *Boswellia*, (BosLiq®), myrrh (MyrLiq®), pineapple and seed oil from *Buglossoides arvensis*. The ability of Evandol to reduce the mean pain score in the treatment group with respect to the control group at the time of IUD insertion offers clear evidence that acute pain can be overcome by priming patients with Evandol prior to IUD insertion. The analgesic properties of Evandol seem to eliminate pain in almost all patients when compared to control group as evidenced by the fact that the pain scores were zero in most of the patients after three days of IUD insertion and the pain score comparisons on day three revealed significant differences between the groups. The results of this study need to be analyzed by further investigations, which should include a larger cohort of patients. Furthermore, follow up studies should involve clinical trials with strict inclusion and allocation strategies.

Conclusions

This pilot observational study about Evandol, a novel herbal mixture, might pave the way for an herbal adjuvant therapy for patients destined to undergo intrauterine device insertion.

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