Non-interventional retrospective study to evaluate menstrual bleeding profiles, tolerability and quality of life of women using the new vaginal ring Ornibel® delivering etonogestrel 0.120 mg and ethinylestradiol (EE) 0.015 mg per day

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Research article

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Abstract

Background: To assess the menstrual cycle profile, tolerability, quality of life and sexual wellbeing in women using the vaginal contraceptive ring Ornibel®.

Method: Non-interventional, retrospective, multi-center study on 103 women between 18 and 45 years old that used Ornibel® for at least 6 months. Menstrual cycle characteristics, vaginal infections and quality of life parameters were analyzed. Change in menstrual bleeding profiles and menstrual bleeding associated pain were assessed via visual analogue scales (VAS).

Results: Menstrual flow and dysmenorrhea reduced significantly. The VAS score reductions were 16 and 22,5 points respectively ($p < 0.001$). No differences were observed between women that changed from another contraceptive method to the vaginal ring. The percentage of women without unscheduled bleedings or spotting increased from 79% to 88%. The percentage of women with unscheduled bleeding or spotting significantly decreased from 21% to 12%. Women rated the ring as very comfortable or comfortable (97%) as well as easy to insert (91%). The continuation of the usage of the ring and a recommendation for the ring were significantly associated with these two parameters.

Conclusions: Ornibel® improved the menstrual cycle profile, reduced dysmenorrhea and shows a very high adherence to the use. Clinical trial register: DRKS-ID: DRKS00014982

Background

Combined oral contraception (COC) have become increasingly popular, due to the low pearl index (PI) and low rate of side effects (1). Anyway, COCs are associated with negative aspects especially due to the oral application form and the estrogenic side effects. This might lead to symptoms like nausea, breast tenderness, weight increase, or thromboembolic events (2). Moreover, orally applied contraception is influenced by disorders of the gastrointestinal tract and must pass by the liver metabolism. Thereby interactions with other medicines become more frequent. In consequence, the efficacy of COC might get reduced (3, 4). Another disadvantage of orally applied COC is the daily intake. This increases the risks of missed pills. (5, 6).

Vaginal ring delivery systems are the answers to many of these complaints. The first available vaginal ring called NuvaRing® is a combined hormonal ring containing 11.7 mg etonogestrel and 2.7 mg ethinylestradiol (EE) and was approved by the FDA in 2001 (7, 8).

The ring releases constantly, with a pharmacokinetic zero order release and without first pass effect on average 0.120 mg of etonogestrel and 0.015 mg of EE daily over a three-week period of use to inhibit ovulation (4, 9) with a pearl index under 1 (0,6) (3, 7, 8, 10, 11). The NuvaRing® consists of two polymers; Evatane® 28 % in the core and Evatane® 9 % in the membrane; this ring is a so-called reservoir ring system (12).

Ornibel® (developed by Laborarios LeonFarma, SA, Chemo Group, Spain) is a new combined contraceptive vaginal ring which has the same size and a similar external appearance to NuvaRing®. Nevertheless, Ornibel® is composed by a core of polyurethane and an external membrane of ethylene vinylacetate, containing 28% vinylacetate. This different polymer composition allows the active ingredients in Ornibel® to be in a concentration below the saturation limit, as opposed to the reference product. An additional advantage is that no special conditions for storage temperature are required. Ornibel® contains the same active pharmaceutical ingredients than NuvaRing® but at a different nominal dose, 11.00mg etonogestrel and 3.47mg ethinylestradiol. Despite this difference in the nominal dosage, the average hormonal release from both rings is the same (13).

The aim of this non-interventional retrospective study was to obtain clinical data of this new vaginal ring. Analyses were performed for the menstrual cycle profile, the tolerability, the quality of life, the infection rate and the adherence to the product even in cases of side effects of this new vaginal ring.

Methods

Study design

Non-interventional, retrospective, multi-center study conducted between October 2018 and May 2019 in 13 centers in Germany. The study was conducted in accordance with the declaration of Helsinki as well as in compliance with local legal and regulatory requirements.

Study medication

Ornibel® (etonogestrel/ethinylestradiol 11.00/3.47 mg, Exeltis Healthcare SA, Spain) was used over 6 months. The recommended posology dosage states that once the ring is inserted, it is left in the vagina continuously for 3 weeks. The ring must be removed after 3 weeks of use on the same day of the week as the ring was inserted and after a ring-free interval of one week a new ring is to be inserted.

Study population

Adult female patients (n = 103) that used Ornibel® as contraceptive, for a minimum of 6 months, were recruited for the study. Women were eligible for the study in case they were aged between ≥18 and ≤45 years, use Ornibel® as contraceptive method for at least 6 months, and gave written signed informed consent. Women with a BMI > 30 kg/m² were excluded from the study.

Further exclusion criteria were women using intrauterine devices (IUD) or intrauterine systems (IUS) and breastfeeding women.

Study procedure

Women were asked to participate in the study when using Ornibel® at least for 6 months. If the patient was using Ornibel® for more than 6 months, the first 6 months of usage were assessed. After written

informed consent, women filled in a questionnaire were the parameters regarding quality of life, menstrual cycle profile and vaginal infections were documented. Demographic data, medical history, concomitant medications and possible (severe) adverse events (S)AE, which occurred during the treatment phase with Ornibel® were recorded.

Study objectives

- ◦ Primary efficacy endpoint

To assess menstrual bleeding profiles and tolerability of women after usage of Ornibel® over an observation period of 6 months.

Secondary efficacy endpoint

1.) Quality of life after usage of Ornibel® for at least 6 months.

2.) Rate of vaginal infections diagnosed by a health care professional.

Statistical Methods

Quantitative and semi-quantitative measurements were tested for normal distribution using the Kolmogorov-Smirnov test. VAS assessment of menstrual flow and pain cramping showed significant deviations from normal distribution, comparisons of treatment times were consequently done using non-parametric Wilcoxon matched pairs test.

Ordinally and nominally scaled values were displayed in absolute and percent frequencies. Two of each of these values were compared in contingency tables and tested for association with the chi-square test or in case of ordinally scaled variables using the chi-squared linear trend test. If the expected frequencies turned out to be too small, exact tests (according to Fisher or exact linear trend test) were used. Comparisons of treatment times were performed using the McNemar test.

All tests were done two sided with significance level of 5%. Statistical analyses were performed using SPSS Statistics 25 (SPSS Inc. an IBM Company, Chicago, IL).

Ethical approval

For each of the investigational centers an ethical approval was obtained. The overall approval for the leading ethical committee was given on 23.07.2018 by the Ethikkommission der Ärztekammer Nordrhein, Germany with the number 2018180. Clinical trial register: DRKS-ID: DRKS00014982. Date of registration: 06.08.2018. The date the first subject entered was 04.10.2018. End of study: 09.05.2019.

Results

Baseline data

Of 103 women that were screened for the study, 100 women were eligible for analysis. One woman was excluded from the study due to BMI and two women did not hand in the filled patient questionnaire (figure 1). Women had a median age of 27 years and a median BMI of 22.5 kg/m² (table 1). None of the women used non-steroidal anti-phlogistics. Previously, women used oral contraceptives (37%), progesterone-only pill (2%), intrauterine device (3%), non-hormonal contraception (6%) or did not use any form of contraception (52%).

Cycle control

During the first 6 months of Ornibel® usage 73 of 100 women experienced 6 menstrual bleedings with a median bleeding duration of 4 days. Menstrual flow and dysmenorrhea significantly reduced after the 6 months of ring use. The median VAS score for the menstrual flow was 50 before the treatment and 34 after treatment ($p < 0.001$) (see figure 2a). Regarding the development of dysmenorrhea also statistically significant improvements could be observed. The median VAS score value was 42.5 before and 20 after the six months ($p<0.001$) (see figure 2b). Both parameters improved especially during the first three months of usage.

The percentage of women without spotting or unscheduled bleeding increased from 79% to 88% after the 6 months use of Ornibel®. In contrast, the number of women that had spotting and/or unscheduled bleeding before the treatment experience a reduction of these events from 21% to 12% ($p<0.022$) (see table 2). Seven women experienced a mild or moderate vaginal infection.

Quality of life

A high rate of women strongly agreed or agreed that Ornibel® was easy to insert (91%). They rated the use of the ring as very comfortable or comfortable (97%). The continuation of the usage of the ring and a recommendation for the ring were significantly associated with these two parameters even for those women belonging to the group that did not agreed in the easiness of ring insertion or comfortability of use (continuation rate: easy to insert: $p = 0.017$; feeling comfortable: $p = 0.001$; recommendation: easy to insert: $p = 0.004$; feeling comfortable: $p = 0.005$).

The daily activities were never affected by the ring in 85% of women. Only 15% of women mentioned that their daily activities were occasionally affected and none of the women rated the interference of the daily activities with frequently or always. There was a significant association between “ring never or occasionally affected my daily activities” and “continuation of usage” ($p = 0.027$) as well as “recommendation for the ring” ($p = 0.023$).

Fifty percent of the partners did not notice the ring during sexual intercourse, 38% occasionally and only 6% of the partners notice the ring frequently or always. Eight women experienced a ring loss, a number that could be expected according to the summary of product characteristics. No association was found for the parameters “Ring was noticed by my partner during sexual intercourse” (continuation of usage: p

= 0.074, recommendation for the ring: 0,108) and “Ring lost during usage” (continuation of usage: p = 0.077, recommendation for the ring: 0.611).

Most women learned from their physician about the ring (81%), will continue the use of the ring (91%) and will recommend the ring (95%) to other women.

Discussion

The basis of an effective contraception involves factors like the possibility of getting access to these methods, the adverse event profile, the mode of use and the ease in this use (4, 14). Careful patient counseling are therefore vital components in improving compliance. Vaginal rings have on one site the advantage to be associated with a reduced efficacy due to miss pill intake (5, 6), on the other side the vaginal route still is an impediment for a wider acceptance (4). The existing vaginal ring NuvaRing is associated with continuation rates between 85.9% to 88.7 % after one year of use. The new ring showed a similar or even better continuation rate after 6 months of 91 %. These data are similar or also even superior to the rates obtained for oral contraceptive systems (2, 7, 8, 11, 15) (table 3).

The rate of break through bleeding is lower when compared to different oral combined formulations. A prospective study has shown that 97% of 2642 women reported regular cycles with the ring. Irregular bleedings were only rarely observed, meaning 12% at baseline level and 7% at final examination (16, 17). Also, the planed withdrawal bleedings were observed in up to 98.5 % of the users with a rate of irregular bleedings or spotting not being higher than in 5.5 % of the investigated cycles (7). In a 1-year survey of 2322 woman with 23.298 cycles, 85% of the users reported to be satisfied with the ring (7). In another investigation of 1950 women, 85% of these women and 71% of the sexual partners never or rarely felt the ring during vaginal sexual intercourse and 94% of the partners never or rarely minded that the woman was using a ring (8). In the case of Ornibel only 6 % of the sexual partners noticed the ring frequently during sexual intercourse. At the same time 98 % of the women documented the ring was easy to insert and this was also the case in 90 % of early discontinuers. With Ornibel similar data were achieved (7, 8).

Data have also shown that ring users have not a risk in an increase of vaginal infections due to the use of such a device (18, 19). The users of the new ring had in accordance to the older data an even lower infection rate. These data support therefore the *in vitro* data of microbiological adherence to the new ring. The *in vitro* low adhesion to candida was reflected in this *in vivo* study (20).

When analyzing the discontinuation rates a clear difference toward Ornibel® can be found. Only 9 % of the women discontinued in comparison to NuvaRing® for which the data where up to 14 %. This could be due to the new polymers used in Ornibel® (see table 3).

Conclusion

The new generation of vaginal contraceptive rings show not only a high efficacy but also a high satisfaction and user comfort for the patients. Even in the case of having adverse events in a small

number of cases these were not a reason for discontinuation in the use of the contraceptive method.

Declarations

Abbreviations

Not applicable

Legends

Table 1: Baseline characteristics of women.

Table 2: Development of unscheduled bleedings or spotting before and after the 6-month treatment with Ornibel ($p < 0,022$).

Table 3: Discontinuation rates between NuvaRing® and Ornibel® in % of the study group.

Figure 1: Consort diagram of the study.

Figure 2: A: Median VAS score values for menstrual bleeding before (blue) and after (red) the 6-month treatment with Ornibel. 75^{th}, 50^{th} and 25^{th} percentile. Median reduction of 16 points ($p < 0.001$). B: Median VAS score values for dysmenorrhea before (blue) and after (red) the 6-month treatment with Ornibel. 75^{th}, 50^{th} and 25^{th} percentile. Median reduction of 22.5 points ($p < 0.001$).

Ethics approval and consent to participate

For each of the investigational centers an ethical approval was obtained. The overall approval for the leading ethical committee was given on 23.07.2018 by the Ethikkommission der Ärztekammer Nordrhein, Germany with the number 2018180. Clinical trial register: DRKS-ID: DRKS00014982. Date of registration: 06.08.2018. The date the first subject entered was 04.10.2018. End of study: 09.05.2019.

Consent for publication

All authors have consented for publication.

Availability of data and material

Clinical trial register: DRKS-ID: DRKS00014982. Date of registration: 06.08.2018. The date the first subject entered was 04.10.2018. End of study: 09.05.2019.

Competing interests

Pedro-Antonio Regidor, Manuela Sailer, Enrique Calvo and Enrico Colli are employees of Exeltis Healthcare. Santiago Palacios and Thomas Römer declare no conflict of interest.

Santiago Palacios is editorial board member of the Journal.

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Authors' contributions

Pedro-Antonio Regidor and Manuela Sailer were responsible for the practical realization of the study.

Enrique Calvo and Enrico Colli wer responsible for the study design

Santiago Palacios was responsible for the co-ordination of the centers and scientific support

Thomas Römer was responsible as principal investigator of the study.

Acknowledgements

Not applicable

References

1.) Regidor PA. The clinical relevance of progestogens in hormonal contraception: Present status and future developments. Oncotarget 2018; 9: 34628–34638.

2.) Brache V, Faundes A. Contraceptive vaginal rings: a review. Contraception. 2010; 82: 418–427.

3.) Lete I, Duenas JL, Esplugues JV, et al. Is the vagina an adequate route for the administration of hormonal contraceptives? Curr Drug Metab. 2010; 11: 839–849.

4.) Wieder DR, Pattimakiel L. Examining the efficacy, safety, and patient acceptability of the combined contraceptive vaginal ring (NuvaRing®. Int J Women´s Health. 2010; 2:401–409

5.) Rosenberg MJ, Waugh MS, Meehan TE. Use and misuse of oral contraceptives: Risk indicators for poor pill taking and discontinuation. Contraception 1995; 51. 283–288.

6.) Rosenberg MJ, Waugh MS, long S. Unintended pregnancies and use, misuse and discontinuation of oral contraceptives. Journal of reproductive medicine 1995; 40: 355–360.

7.) Dieben TO, Roumen FJ, Apter D. Efficacy, cycle control and user acceptability of a novel combined contraceptive vaginal ring. Obstet Gynecol. 2002; 100:585–593

8.) Roumen FJ, Apter D, Mulders TM, Dieben TO. Efficacy, tolerability and acceptability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl oestradiol. Hum Reprod. 2001; 16:469–475

9.) Mulders TM, Dieben TO. Use of the novel combined contraceptive vaginal ring NuvaRing for ovulation inhibition. Fertil Steril. 2001 May;75(5):865–70

10.) Creinin MD, Meyn LA, Borgatta L, et al. Mulitcenter comparison of the contraceptive ring and patch. Obstet Gynecol. 2008; 111:267–277

11.) Ahrendt HJ, Nisand I, Bastianelli C, Gómez MA, Gemzell-Danielsson K, Urdl W, Karskov B, Oeyen L, Bitzer J, Page G, Milsom I. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 microg of ethinyl estradiol and 3 mg of drospirenone.Contraception. 2006 Dec;74(6):451–7. Epub 2006 Sep 27.

12.) Timmer CJ, Mulders TM. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptivevaginal ring. Clin Pharmacokinet. 2000 Sep;39(3):233–42.

13.) Algorta J, Diaz M, de Benito R, Lefebvre M, Sicard E, Furtado M, Regidor PA, Ronchi C. Pharmacokinetic bioequivalence, safety and acceptability of Ornibel®, a new polymer composition contraceptive vaginal ring (etonogestrel/ethinylestradiol 11.00/3.474 mg) compared with Nuvaring® (etonogestrel/ethinylestradiol 11.7/2.7 mg). Eur J Contracept Reprod Health Care. 2017 Dec;22(6):429–438.

14.) Westhoff CL, Torgal AH, Mayeda ER, Petrie K, Thomas T, Dragoman M, Cremers S. Pharmacokinetics and ovarian suppression during use of a contraceptive vaginal ring in normal-weight and obese women. Am J Obstet Gynecol. 2012 Jul;207(1):39.e1–6. doi: 10.1016/j.ajog.2012.04.022. Epub 2012 Apr 28.

15.) Oddsson K, Leifels-Fisher B, Melo NR, Weil-Masson D, Benedetto C, Verhoeven CHJ. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial. Contraception 2005; 71. 176–182.

16.) Merki-Feld GS, Hund M. Clinical experience with NuvaRing in daily practice in Switzerland: cycle control and acceptability among women of all reproductive ages. Eur J Contracept Reprod Health Care 2007; 12:240–247

17.) Brucker C, Karck U, Merkle E. Cycle control, tolerability, efficacy and acceptability of the vaginal contraceptive ring, NuvaRing: results of clinical experience in Germany. Eur J Contracept Reprod Health Care. 2008 Mar;13(1):31–8.

18.) Davies GC, Feng LX, Newton JR, Dieben TO, Coelingh-Bennink HJ. The effects of a combined contraceptive vaginal ring releasing ethinyloestradiol and 3-ketodesogestrel on vaginal flora. Contraception. 1992 May;45(5):511–8

19.) Roumen FJ, Mishell DR Jr. The contraceptive vaginal ring, NuvaRing(®), a decade after its introduction. Eur J Contracept Reprod Health Care. 2012 Dec;17(6):415–27. doi: 10.3109/13625187.2012.713535. Epub 2012 Oct 31. Review

20.) Sailer M, Colli E, Regidor PA. In vitro evaluation of microbial adhesion to a contraceptive vaginal ring with a new polymer composition. Eur J Contracept Reprod Health Care. 2019 Jun;24(3):188–191. doi: 10.1080/13625187.2019.1595575. Epub 2019 Apr 12.

Tables

Table 1: Baseline characteristics of women.

	Mean ± SD
Age [years]	28.64 ± 7.49
Height [cm]	167.70 ± 6.89
Weight [kg]	65.31 ± 11.44
BMI [kg/m²]	23.18 ± 3.37
Heart rate	73.53 ± 6.40
Blood pressure [mmHg]	
Systolic	118.84 ± 10.84
Diastolic	74.83 ± 8.69

Table 2: Development of unscheduled bleedings or spotting before and after the 6-month treatment with Ornibel ($p < 0{,}022$).

			Bleedings between periods during treatment		Total
			no	yes	
Bleedings between periods before treatment	no	Count	77	2	79
		% of Total	77.0%	2.0%	79.0%
	yes	Count	11	10	21
		% of Total	11.0%	10.0%	21.0%
Total		Count	88	12	100
		% of Total	88.0%	12.0%	100.0%

					Dieben et al. 2002		Oddison et al. 2005		Ahrend et al. 2006		Evol Study
					NuvaRing®		NuvaRing®		NuvaRing®		Ornibel®
	Discontinuation due to AE				14.1		11.3		12.3		9
	Discontinuation due to device-related events				2.5		2.1		3		1
	Discontinuation due to headache				1.3		0.8		1		0
	Ring related vaginitis				4.4		4.7		6.8		1
	Nausea				3.2		2.7		0.8		0
	Headache				5.8		7.2		6.8		0

Table 3: Discontinuation rates between NuvaRing® and Ornibel® in % of the study group.

					Dieben et al. 2002		Oddison et al. 2005		Ahrend et al. 2006		Evol Study
					NuvaRing®		NuvaRing®		NuvaRing®		Ornibel®
	Discontinuation due to AE				14.1		11.3		12.3		9
	Discontinuation due to device-related events				2.5		2.1		3		1
	Discontinuation due to headache				1.3		0.8		1		0
	Ring related vaginitis				4.4		4.7		6.8		1
	Nausea				3.2		2.7		0.8		0
	Headache				5.8		7.2		6.8		0

Figures

Figure 1: Consort diagram of the study.

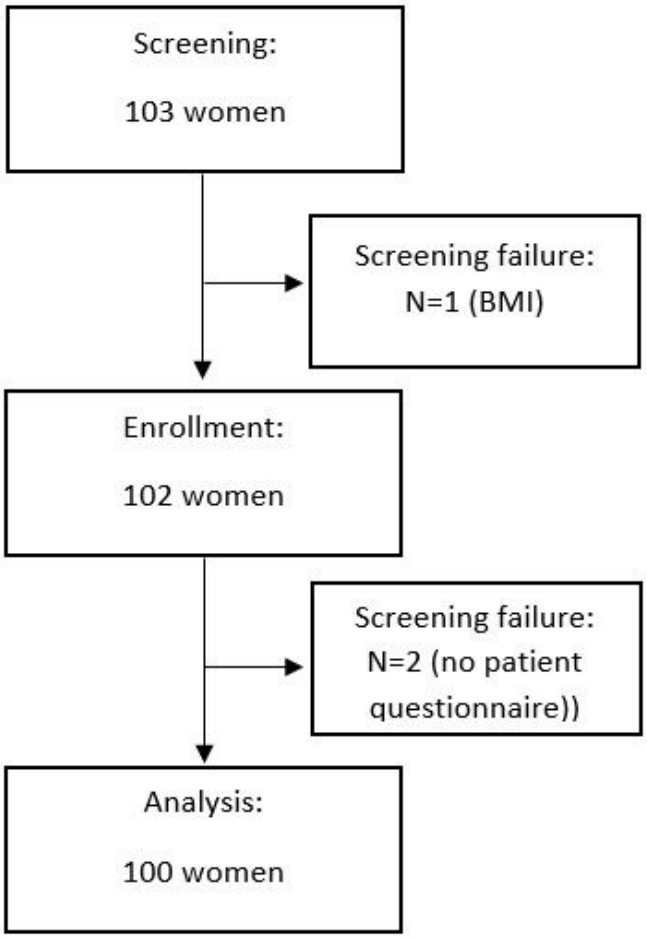

Figure 1

Consort diagram of the study.

Figure 2: A: Median VAS score values for menstrual bleeding before (blue) and after (red) the 6-month treatment with Ornibel. 75th, 50th and 25th percentile. Median reduction of 16 points ($p < 0.001$). B: Median VAS score values for dysmenorrhea before (blue) and after (red) the 6-month treatment with Ornibel. 75th, 50th and 25th percentile. Median reduction of 22.5 points ($p < 0.001$).

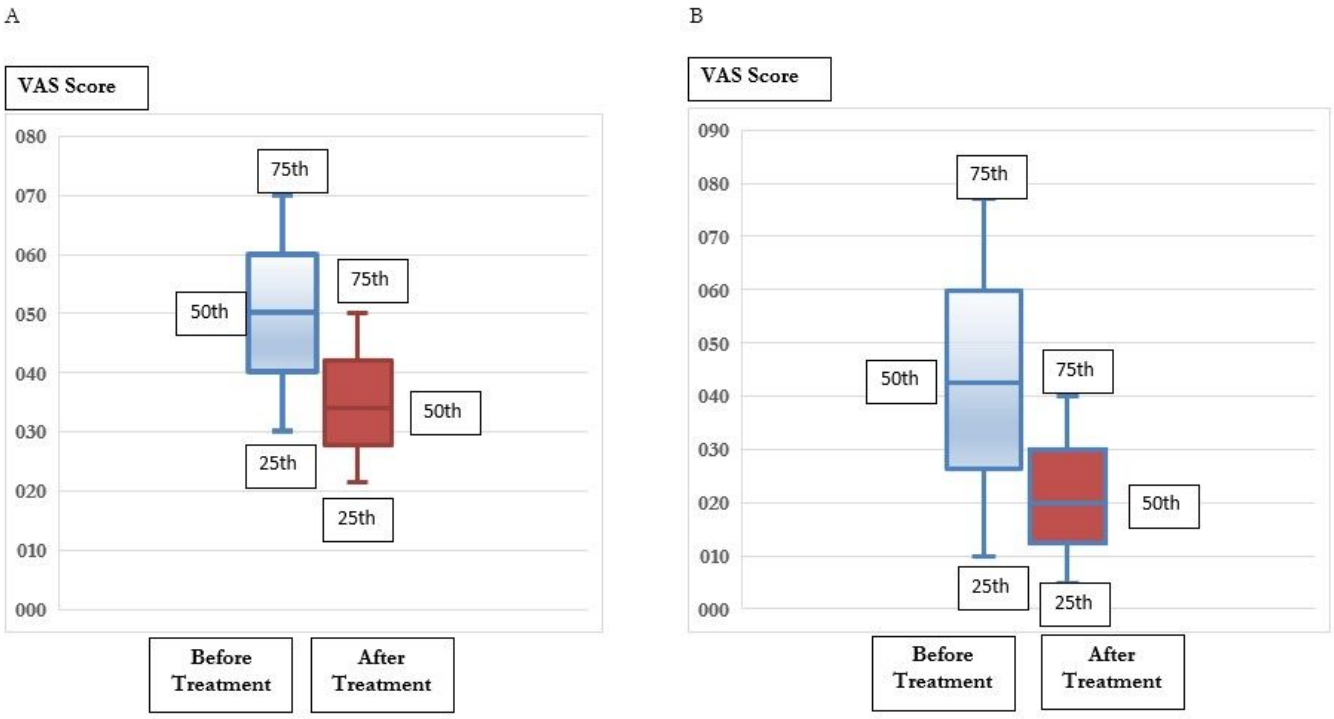

Figure 2

A: Median VAS score values for menstrual bleeding before (blue) and after (red) the 6-month treatment with Ornibel. 75th, 50th and 25th percentile. Median reduction of 16 points ($p < 0.001$). B: Median VAS score values for dysmenorrhea before (blue) and after (red) the 6-month treatment with Ornibel. 75th, 50th and 25th percentile. Median reduction of 22.5 points ($p < 0.001$).