

Treatment of menorrhagia with a novel “frameless” intrauterine levonorgestrel-releasing drug delivery system: a pilot study

D. Wildemeersch*, E. Schacht**

*Control Research, Technology Park Zwijnaarde, Ghent, Belgium

**Polymer Research Group, University of Ghent, Department of Chemistry, Ghent, Belgium

ABSTRACT

Objective To evaluate the effect on menstrual blood loss of a novel “frameless” intrauterine drug delivery system (IUS), FibroPlant-levonorgestrel (LNG), releasing 14µg of LNG/d. An ancillary objective being to evaluate the contraceptive performance.

Study design An open label, non-comparative ongoing pilot study. Thirty-two insertions were performed in fertile women between 31 and 51 years of age for the treatment of menorrhagia as well as for contraceptive purposes. Fifteen women were fitted with the FibroPlant-LNG IUS immediately following removal of a copper-bearing IUD, the GyneFix IUD, who developed excessive bleeding. To discriminate between menorrhagia and normal menstrual blood loss, women were evaluated using a simple visual assessment technique. The trial covers a period from a minimum of 1 month up to 23 months.

Results At the time of study analysis the total number of women-months was 361. Fourteen women having the FibroPlant-LNG IUS in place for periods in excess of one year and twenty-nine women for 6 months or more. All women reported greatly reduced bleeding. However, no cases of amenorrhea resulting from endometrial suppression were encountered. The reduction of bleeding was appreciable after one month of treatment and decreased further over the next months to remain stable afterwards. The mean bleeding score before treatment was 338 (185-740) in the group with no prior IUD use and 368 (185-890) in the group with prior IUD use, respectively, and dropped to a mean score of 70 (range 5-210) in the 'no prior IUD use' group and to a mean score of 52 (3-150) in the 'prior IUD use' group, respectively after 1 to 23 months follow-up which is highly statistically significant ($p < 0.001$). There was no statistical difference in bleeding scores before and during treatment between the two groups of women with or without prior copper IUD use.

Significant spotting was rare after the first three months following insertion. Neither complications (e.g., infection, expulsion or perforation) nor pregnancies occurred. The FibroPlant-LNG IUS was well tolerated by all women involved in the study and no systemic hormonal side effects were reported.

Conclusion FibroPlant-LNG IUS is effective to significantly reduce the amount of menstrual blood loss in women with menorrhagia. The strong endometrial suppression is the principal mechanism explaining both the effect on menstrual blood loss and the contraceptive performance of the IUS. There was no difference in bleeding scores before and during treatment between two groups of women with or without prior copper IUD use, suggesting that the development of heavy bleeding was not related to the use of the IUD.

The therapeutic effect of this contraceptive method is highly desirable, particularly in women with heavy bleeding or anemia in developing countries, as other treatment modalities are less effective, more costly, more invasive or inaccessible.

The low daily release rate of levonorgestrel from the FibroPlant-LNG IUS results in a low incidence of hormonal side effects and in reducing the likelihood of amenorrhea.

The simple design characteristics and revolutionary anchoring system account for minimising the occurrence of complaints of pain and expulsion.

KEY WORDS: “Frameless” intrauterine system (IUS), Levonorgestrel (LNG), contraception, menorrhagia, pilot study

Name and address for correspondence: Dr. Dirk Wildemeersch, Piers de Raveschootlaan 125, 8300 Knokke, Belgium. Tel: (32)50-600900; Fax: (32)50-622429
Email: dirk.wildemeersch@contrel.be. Website: www.contrel.be

INTRODUCTION

Menorrhagia, defined as regular but heavy menstrual bleeding of more than 80 ml from a secretory endometrium is a common disorder. The prevalence is between 9% and 28% of women aged 16-45 years and increases with age.¹ Approximately 30% of patients referred for gynecological treatment are for menorrhagia, often leading to surgical intervention if conservative treatment (e.g. contraceptive pills, progestogens, fibrinolytic inhibitors and prostaglandin inhibitors) fails. In the USA, 700,000 hysterectomies are performed each year of which 30% for excessive menstrual bleeding. In the UK 40% of the 100,000 hysterectomies are performed for that reason. Idiopathic menorrhagia is the most common form of menorrhagia when no underlying cause (e.g. uterine and endometrial abnormalities, systemic coagulation defects) can be found. Local defects in the haemostatic mechanism in the endometrium are most probably at the origin of the disorder such as an increased fibrinolytic activity or an imbalance in the different types of prostaglandins.²

When menstrual blood loss exceeds 80 ml, the incidence of anemia (haemoglobin less than 12 g/dl) is increased significantly.³ Anemia is one of the most widespread, and most neglected, nutritional deficiency diseases in the world today.⁴ Iron deficiency with depletion of iron stores and/or anemia predisposes the women to ill health and disease. In addition, women with menorrhagia are often prevented from leading normal lives causing severe social embarrassment and repudiated by the partner.

Recently, new less invasive treatment options have been developed.⁵ Endometrial ablation techniques and classical endometrial resection have their value but are still very costly although significantly cheaper than hysterectomy. They are also irreversible. The intrauterine system releasing 20 µg of levonorgestrel (Mirena[®] LNG 20-IUS) has shown a dramatic decrease in menstrual blood loss in nearly all women and amenorrhea in up to 20% or more due to profound endometrial atrophy.⁶⁻⁸

This paper reports on the results in women with menorrhagia using a new "frameless" levonorgestrel-releasing drug delivery system, the FibroPlant-LNG intrauterine system. The physical design of FibroPlant-LNG IUS has been optimized in order to provide optimal tolerance and avoid incompatibility problems. FibroPlant-LNG releases a lower dosage of levonorgestrel (14 µg/day) than the Mirena[®] IUS (20 µg/day) and could result in an overall low rate of hormonal side effects, less effect on ovarian function and minimize the occurrence of amenorrhea.

Previous clinical studies conducted with the FibroPlant-LNG IUS have demonstrated the endometrial suppressive effects of FibroPlant-LNG in perimenopausal and postmenopausal women during estrogen replacement therapy and its contraceptive performance in fertile women.^{9,10}

MATERIALS AND METHODS

Description of the FibroPlant-LNG IUS

The FibroPlant-LNG IUS uses the standard GyneFix[®] anchoring system but has no copper tubes attached to the thread. The copper tubes being replaced by a 4-cm long and 1.2 mm wide fibrous delivery system that releases approximately 14 µg of LNG daily. The fibrous delivery system is fixed to the anchoring thread by means of a metal clip positioned 1 cm from the anchoring knot.

In vitro studies show that the rate of LNG release is constant over several years. The duration of release, calculated by extrapolation, is approximately 3 years but may be longer in vivo. The fibrous delivery system was developed in collaboration with the Polymer Research Group, Department of Chemistry, University of Ghent, Ghent, Belgium.

In common with GyneFix[®], the anchoring knot at the proximal end of the thread is implanted into the myometrium of the uterine fundus using the standard GyneFix[®]

insertion instrument, thus permanently securing the implant in the uterine cavity (Figure 1).

The stainless steel metal clip allows ultrasound and X-ray visibility of the system thus enabling correct location of the system in the uterine cavity, both at insertion and at follow-up. The fibrous delivery system is also visible on ultrasound (Figure 2).

Measuring the distance between the surface of the uterus and the metal clip (S-S distance) indicates whether the FibroPlant IUS has been properly anchored.

When compared with the Mirena[®] LNG IUS, the FibroPlant-LNG IUS has no frame, it is therefore completely flexible, with the ability to adapt to uterine cavities of every size and shape.

Screening and selection

All women to be included in the study were screened for both their clinical suitability for IUD insertion and in accordance with the WHO eligibility criteria. The following were excluded: use of any other form of contraception; clinical cervicitis or vaginitis (infection should be ruled out); sound length greater than 10 cm; history of PID, genital actinomycosis or chronic pelvic pain; blood clotting disorder; known or suspected uterine or cervical malignancy; detectable congenital malformation of the vagina, cervix or uterus; postpartum endometritis or history of infected abortion; leukemia; currently receiving corticosteroid or immunosuppressive therapy; congenital valvular heart disease.

Only women with idiopathic menorrhagia were selected to participate in the study. Women developing excessive bleeding during the use of a copper IUD were also included, as were women with small subserous or intramural fibroids less than 3 cm in diameter. Vaginal ultrasound examination (Ultramark[®] 4Plus, ATL Inc., USA) was performed to exclude major uterine pathology.

To discriminate between menorrhagia and normal menstrual blood loss, a simple visual assessment technique was used as described by A.H. Janssen.³ Information on menstrual bleeding was obtained by interview prior to entering the study using a pictorial chart form to describe the degree to which the sanitary wear was soiled. A score was calculated by multiplying the number of slightly, moderately and heavily soiled pads and tampons by one, five and 20 for pads and one, five and 10 for tampons, respectively, according to their degree of staining (Figure 3). It should be noted that no standard type of sanitary material was used. In this context, the pictorial chart method as used in this study would seem to be unreliable. However, even if women used 'maxi' pads or 'super' tampons, the calculation was based on the lowest value as they were using normal sanitary wear. Women with menorrhagia wish to use 'maxi' pads or 'super' tampons, or even 'double' protection, during their 'heaviest' days, and then switch to normal pads and tampons when the amount of bleeding decreases. A score of 185 was used as cutoff point as this score has a predictive value of 85% to be consistent with menorrhagia.³

Admission and insertion of the IUS

One investigator (DW) performed all insertions. Written informed consent was obtained and the Ethics Committee of the Ghent University, Belgium, approved the study. Patients were checked for any clinical signs of sexually transmitted diseases. Routine chlamydia tests were not carried out as those women included in the study were at low risk for sexually transmitted infections (STIs).

Insertion of the FibroPlant IUS is identical to that for the insertion of the GyneFix[®] implant system.¹¹ Following insertion, vaginal ultrasound was performed to locate the device in the uterus as described previously.

Follow-up

Women were followed-up at 1, 3, 6, and 12 months following insertion of the FibroPlant-LNG IUS and 6-monthly thereafter. During follow-up women were interviewed about their bleeding patterns and any side effects or adverse reactions. On each occasion a full gynecological examination including vaginal ultrasound was performed to exclude any abnormalities and to locate the implant.

To measure the effect of FibroPlant-LNG IUS on the amount of menstrual blood loss, the pictorial chart form was completed. The purpose of this simple evaluation was to obtain clinical measurable information of the effect of the FibroPlant-LNG IUS on the amount of bleeding on an individual basis.

RESULTS

Thirty-two women, fitted with FibroPlant-LNG, who complied with the study criteria, were examined between 19 November 2000 and 18 January 2001. Fourteen women had the FibroPlant-LNG IUS in place for periods in excess of one year and twenty-nine for 6 months or more. At the time of study analysis the total number of women-months was 361. The events were evaluated on an individual basis. Women were split in two groups: those with prior use of a copper IUD (all women in this group used the GyneFix IUD) and those without prior use of a copper IUD. Although the numbers are small, statistical analysis was carried out according to the method of statistical analysis of variance for repeated measurements, $p < 0.05$ denoting statistical significance.¹² Tables 1 and 2 show the characteristics of the total group. Table 3 and Figures 4 and 5 show the bleeding scores, before and during treatment in the group with prior IUD use ($n=15$) and in the group without prior IUD use ($n=17$).

All women reported greatly reduced bleeding, however no cases of amenorrhea resulting from endometrial suppression were encountered. In most cases, the reduction of bleeding was appreciable after one month and decreased further over the next few months but remained stable afterwards. The mean bleeding score before treatment was 338 (185-740) in the group with no prior IUD use and 368 (185-890) in the group with prior IUD use, respectively, and dropped to a mean score of 70 (range 5-210) in the 'no prior IUD use'

group and to a mean score of 52 (3-150) in the 'prior IUD use' group, respectively after 1 to 23 months follow-up which is highly statistically significant ($p < 0.001$). There was no statistical difference in bleeding scores before and during treatment between the two groups of women with or without prior copper IUD use.

Four women had small fibroids but responded well to the treatment. Those women with the highest score prior to the treatment also had the highest scores during treatment follow-up. The highest score (890) was recorded in a woman who was using a copper IUD. After one month the score dropped to 150. Another women had a pre-treatment score of 515 and kept a high score of 210 after 13 months of treatment. However, the result was highly satisfactory for the patient as she could switch from 'maxi' pads to 'normal' pads and feel comfortable overnight.

All insertions were successful. Significant spotting was rare in the majority of women after the first three months following insertion. Neither complications (e.g., infection, expulsion or perforation) nor pregnancies occurred. The FibroPlant-LNG IUS was well tolerated by all women involved in the study and no systemic hormonal side effects were reported. At the time of study analysis, all women are continuing to use the method.

DISCUSSION

Menorrhagia increases significantly with age. Although menorrhagia is frequent in young women, the percentage of women with menorrhagia is significantly higher above 40 years of age.¹³ This is mainly explained by the higher frequency of uterine pathology, such as fibroids and polyps, which are more common during the premenopausal years. However, in 50% of women with menorrhagia, no gross pathology can be demonstrated.¹⁴ This seems to be confirmed in the present study. A significant rise in the incidence of anemia and low serum ferritin levels occurs mostly several years after the beginning of the condition as it takes some time for the iron stores to become depleted. As more than half of women in this study were taking iron supplementation at study enrollment, the effect of treatment on haemoglobin and ferritin levels was not studied. Besides, the main purpose of the study was to evaluate the effect of endometrial suppression with a low-dose levonorgestrel intrauterine system on the amount of menstrual blood loss using the practical visual assessment scoring technique as described by Janssen et al.³ This pictorial chart method is superior to a woman's subjective assessment of heavy periods. When the score is >185 , bleeding is likely to result in anemia.

The results of the present study are in agreement with those obtained with the Mirena[®] LNG IUS.^{6,7,14-21} The reduction of menstrual blood loss is at least 80% after insertion of the FibroPlant-LNG IUS in women with normal uterus which is highly significant. This occurs as early as one month after the start of the treatment due to strong endometrial suppression. Although approximately half of women in this study were copper IUD wearers prior to insertion of the LNG IUS, there was no difference in score at the start of treatment when compared with the non IUD users suggesting that the development of menorrhagia was unrelated to the presence of the IUD.

Lähtenmäki et al. demonstrated that the LNG IUS (Mirena[®]) can replace hysterectomy due to menorrhagia.²⁰ Two thirds of women involved in his study cancelled their decision to undergo hysterectomy because the treatment was successful. The median number of days of bleeding decreased from seven in the first month to three in the sixth month and two in the twelfth month. It was concluded that treatment of menorrhagia with the LNG-delivery system should be considered before hysterectomy is chosen.

The results of this preliminary study also suggest that the FibroPlant-LNG IUS, releasing 14 µg of LNG per day, provides effective contraception. This confirms a previously conducted studies with the IUS.^{9,10}

For these reasons, the LNG IUS is probably the most effective, non surgical and reversible treatment method of menorrhagia today and the best contraceptive choice in women with anemia. Women are highly satisfied with the results even if irregular bleeding/spotting occurs during the first few months following insertion of the IUS. No women requested removal of the FibroPlant IUS for this reason probably because they were counseled on beforehand.

Women needing contraception and complaining of heavy menses will particularly benefit from intrauterine delivery of LNG. Intermenstrual bleeding and spotting can be minimised by inserting the FibroPlant-LNG IUS during menses or shortly thereafter.

The FibroPlant-LNG IUS, releasing 14 µg of levonorgestrel per day, was developed to provide a strictly localised contraceptive effect and thus minimise systemic hormonal side effects and amenorrhea. Amenorrhea, as defined by absence of bleeding during a period of three months, occurs in up to 25 % of women wearing the Mirena[®] LNG IUS that releases significantly more LNG per day (20 µg). Although it can be looked upon as beneficial to health, amenorrhea also leads to discontinuation of the method in a significant number of women as a result of anxiety and cultural non-acceptance.^{6,7,17} Although some women in the present study came close to amenorrhea, no cases were seen.

Another possible advantage of the low-dosage FibroPlant IUS is the low incidence of hormonal side effects such as acne, mood changes, headache, sleepiness, mastalgia, nausea, and hirsutism which are more likely when higher levonorgestrel doses are used.^{8,22}

The FibroPlant-LNG IUS, has a simple physical design avoiding incompatibility problems seen with both conventional IUDs and the Mirena[®] T-shaped LNG-IUS. Together with its beneficial effects on menstrual blood loss and its high contraceptive performance, FibroPlant-LNG IUS maybe a highly attractive cost-effective treatment option to women in developed and developing countries, and avoid the high cost of surgery and other more invasive treatment procedures such as endometrial ablation, even if the uterus is enlarged (e.g. adenomyosis) or in the presence of small intramural and subserous fibroids.

Conclusion

FibroPlant-LNG IUS is effective to significantly reduce the amount of menstrual blood loss in women with menorrhagia. The strong endometrial suppression is the principal mechanism explaining both the effect on menstrual blood loss and the contraceptive performance of the IUS. There was no difference in bleeding scores before and during treatment between two groups of women with or without prior copper IUD use, suggesting that the development of heavy bleeding was not related to the use of the IUD.

The therapeutic effect of this contraceptive method is highly desirable, particularly in women with heavy bleeding or anemia in developing countries, as other treatment modalities are less effective, more costly, more invasive or inaccessible.

The low daily release rate of levonorgestrel from the FibroPlant-LNG IUS results in a low incidence of hormonal side effects and in reducing the likelihood of amenorrhea.

The simple design characteristics and revolutionary anchoring system account for minimising the occurrence of complaints of pain and expulsion.

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FIGURES

Figure 1. The FibroPlant-LNG IUS (left) and FibroPlant-LNG IUS (right) after insertion in a uterine model.

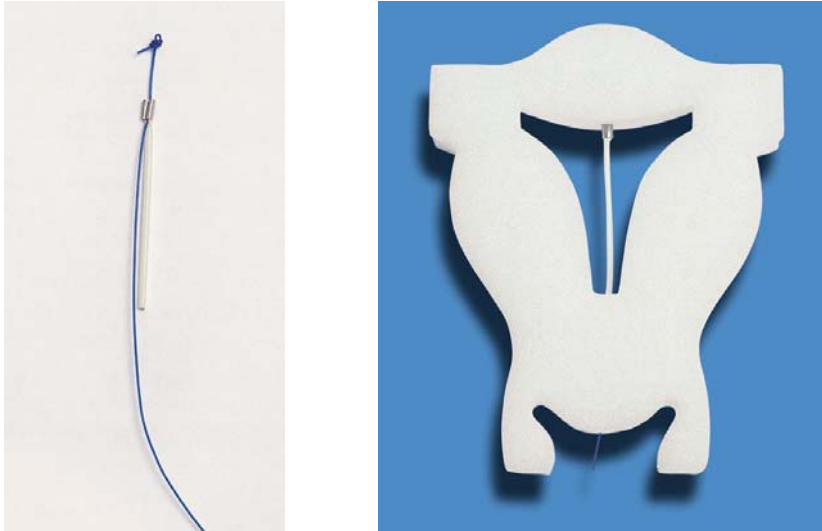


Figure 2. Ultrasound picture of FibroPlant-LNG in situ.

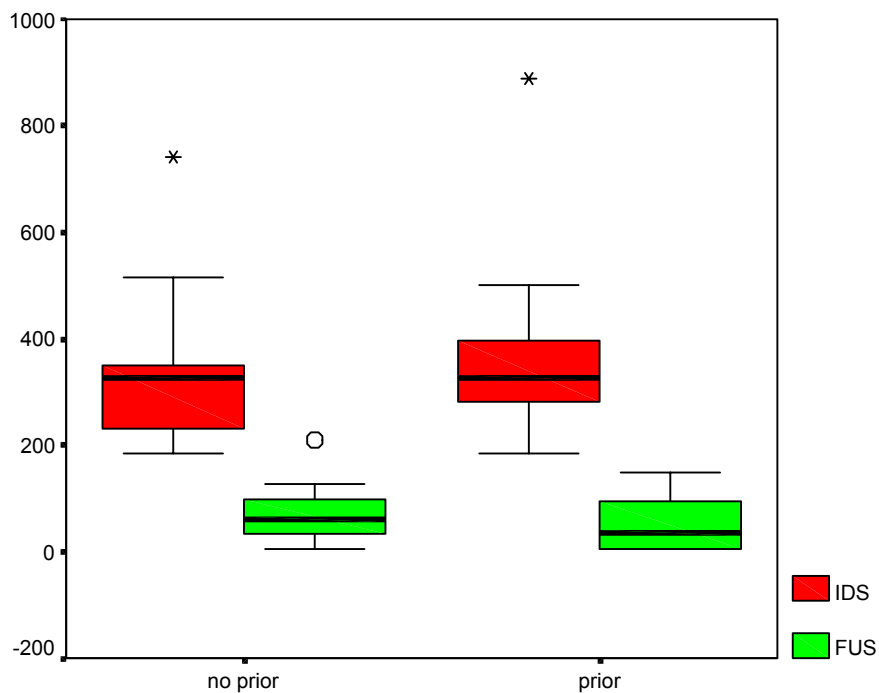


Figure 3. The pictorial chart form. The numbers 1-8 represent the consecutive days of a bleeding episode.

TOWEL	1	2	3	4	5	6	7	8
CLOTS								

TAMPON	1	2	3	4	5	6	7	8
CLOTS								

Figure 4. Mean visual bleeding scores and standard deviation in the two groups of women with no prior IUD use and with prior IUD use, before and during treatment (IDS=bleeding score before treatment; FUS=bleeding score during treatment).



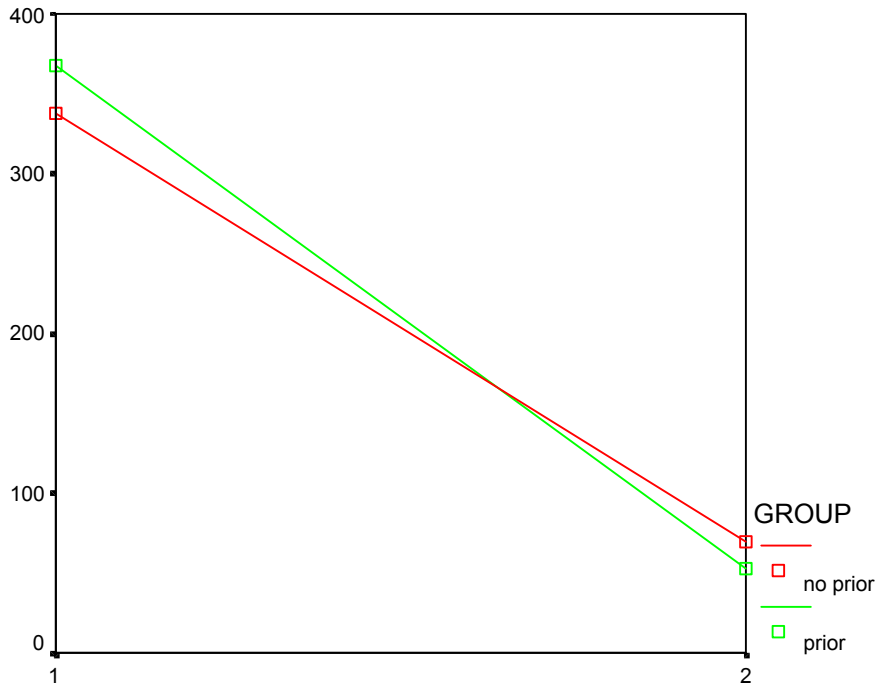
Paired test within each group separately :

Wilcoxon matched-pairs signed-rank test :

‘no prior IUD use’ group : **P < 0.001**

‘prior IUD use’ group : **P < 0.001**

Figure 5. Illustration of the very strong decrease of the scores from 'before' to 'during' ($P < 0.001$), but no difference between both study groups ($P = 0.31$) (No prior=no prior IUD use; Prior=prior IUD use).



TABLES

Table 1. Characteristics of the FibroPlant IUS users (N=32): Age distribution

Mean Age	43
Lowest Age	31
Highest Age	51
Age < 40	23 (71%)
Age > 40	9 (28%)

Table 2. Characteristics of the FibroPlant IUS users (N=32): Gravidity/Parity distribution

	n	%
0	5	16
>0	27	84

Table 3. Analysis of the Visual Bleeding Scores comparison between the group with prior IUD use (n = 15) and the group with NO prior IUD use (n = 17). A. Before treatment. B: During treatment

A. Before treatment

	No prior IUD use	Prior IUD use
n	17	15
Mean	337.9	368.0
St. Dev.	139.2	172.0
Median	324.2	328.8
Q1	229.3	246.7
Q3	358.8	440.0
Minimum	185	185
Maximum	740	890

Mann-Whitney U-test : P = 0.63 (NS)

B. During treatment

	No prior IUD use	Prior IUD use
n	17	15
Mean	70.0	52.3
St. Dev.	52.8	51.3
Median	62.5	41.3
Q1	29.4	5.1
Q3	100.0	103.7
Minimum	5	3
Maximum	210	150

Mann-Whitney U-test : P = 0.31 (NS)