Report on an exploratory study with ActiGel in women with vaginal discomfort

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Introduction

In recent years, vaginal disorders such as vaginitis/vaginosis which are accompanied by vaginal itching and/or abnormal discharge are increasing. These disorders are often caused by intermediation with microorganisms like Candida albicans and Trichomonas vaginalis. Abnormal growth of usual microbes (bacteria) e.g. E. coli, staphylococci and streptococci can cause inflammatory symptoms also leading to vaginal discharge, itching and amine odor and, recently, women complaining of the disorders due to such microbes are increasing. Previously, the latter was categorized as non-specific vaginosis but it is presently known as bacterial vaginosis (BV)[1)].

BV is not a vaginitis but a vaginosis because, unlike candidiasis or trichomoniasis, it causes no strong inflammatory response and the subjective symptoms are rather less. BV is characterized by such findings as multiple bacteria around the epithelial cells (clue cells), a vaginal pH value of more than 5 and fishy amine odor. When the vacteria involved in BV spread upwardly, they can induce salpingitis and pelvic peritonitis. In pregnant women, they can be associated with chorioamnionitis (CAM) leading to premature labor or neonatal infections such as pneumonia, meningitis, etc.[2)]

The number of women complaining of BV-related vaginal discomforts is increasing, and when inflammatory findings are observed justifying the diagnosis "vaginitis" an active therapeutic treatment is recommended. Still, many cases are diagnosed with the old term "non-specific vaginitis". According to the patient survey conducted by the Japanese Ministry of Health, Labor and Welfare in 2008, the estimated number of

patients with candidiasis is reported to be 53 per 1000 women[3], and it is supposed that the number of BV-patients is more than this incidence. It is reported that 30% of pregnant women are affected with BV because of the change in the vaginal hormonal environment[4]. Thus, BV-cases include those who present no inflammatory symptoms and it is important to take actions in advance to prevent a vaginosis to exacerbate into a vaginitis.

In consideration of the diversified social environment of women, the rate of women suffering from vaginal discomforts is supposed to be more than 20% in Japan. Encouraged by a clinical report[5] published in Europe which demonstrates that Multi-Gyn™ ActiGel ("ActiGel"), an acidic vaginal gel based on a high molecular, multi-branched polysaccharide complex, was effective for BV, we were given an opportunity to clinically use ActiGel in order to explore whether it is really applicable to women complaining of vaginal discomforts. This is the report of the exploratory clinical study.

1. Material and Method

The study was conducted in 5 clinics in Tokyo (4 specialized for gynecological diseases and the other 1 for infertility) in women complaining of vaginal discomforts. Ten samples of ActiGel were distributed to each of the 5 clinics aiming at 10 cases per clinic.

Before enrolled in the study, each patient was asked about the history (anamnesis) of vaginal discomforts, the frequency of occurrence and the treatment history. Then, the property of ActiGel, expected efficacy and possible adverse effects were duly explained to the patients. Only those who consented to participation in the study were enrolled in the study.

The study duration was 3 months from October 2012 to January 2013.

2. Pre-treatment history of vaginal discomforts

The completed investigation form was retrieved from all 50 cases by the end of January 2013. The ages of the patients enrolled in the study varied from 21 to 61

years old (mean: 37.0 ± 9.0).

With regard to the history of vaginal discomforts, 41 patients (82.0%) had experienced such discomforts in the past. The other 9 cases (18.0%) did not have such history. Out of the 41 experiencers, 10 patients (24.4%) had been diagnosed with BV, 14 (34.1%) with candida vaginitis and 19 (46.3%) with other discomforts like vulval pruritus, etc. (Table 1). Two patients had experienced concurrently BV and candida vaginitis.

Table 1: History of vaginal discomforts

Diagnosis	No. of cases	Percentage
History of vaginal discomforts	41 cases	100%
-Bacterial vaginosis (BV)	(10)	(24.4%)
-Candida vaginitis	(14)	(34.1%)
-Others	(19)	(46.3%)

With regard to the frequency of occurrence of vaginal discomforts, 20 patients (48.8%) had experienced discomforts a few times a year, 9 (22.0%) developed chronic discomforts (more than 6 times a year) and 12 (29.3%) were uncertain about the frequency (Table 2). Out of the 14 cases of candida vaginitis, 5 (35.7%) were chronic. Out of the other 27 cases diagnosed with BV or others, 4 (14.8%) were chronic. However, no significant difference was seen between these two percentages.

Table 2: Frequency of occurrence of vaginal discomforts

Frequency	A few times a year	Chronically (≧6 times a year)	Uncertain	Total
No. of cases (%)	20 (48.7%)	9 (22.0%)	12 (29.3%)	41 (100%)

3. Assessment of vaginal discomforts at the start of treatment with ActiGel

The degree of vaginal discomforts was assessed as follows: 0 point = “no symptom”; 1-3 points = “mild”; 4-7 points = “moderate”; 8-10 points = “severe”. At the start of treatment, the severity of the symptoms and the percentage of patients were as follows: 2 patients (4.0%) showed no symptoms; 15 (30.0%) showed “mild”; 20 (40.0%) showed “moderate” and 15 (26.0%) did “severe” symptoms (Table 3). The

reason why 2 cases without symptoms were included in the study is that one case had a history of BV and complained of vaginal discomforts 1-2 times a year and the other case sometimes felt vaginal itching and discharge and although neither anamnesis nor present symptoms were found, she strongly proposed to be included in the study.

Table 3: Pre-treatment degree of vaginal discomforts

Degree	No symptom	Mild	Moderate	Severe	Total
No. of cases	2	15	20	13	50
%	4.0	30.0	40.0	26.0	100

4. Therapeutic results

The 50 participants who showed the severity of vaginal discomforts as shown in Table 3 were given one sample of ActiGel and asked to use it every day as instructed and, at the next visit to the clinic, they were interviewed to tell the results and effects of the application of ActiGel. The mean dosing period was 10.7±4.4 days (3 - 21 days) and the application frequency was once or twice a day. The mean dosing period was calculated for only 33 patients who correctly recorded the dates in the investigation form.

Table 4 shows the post-treatment changes in the degree of vaginal discomforts compared with the pre-treatment degrees in 48 patients excluding the 2 cases who presented no symptom before treatment. If one's pre-treatment discomfort score is reduced to zero point, the case was evaluated as "disappearance"; if the score is reduced anyhow, the case was evaluated as "improvement"; if the score remained unchanged, the case was evaluated as "no change". As shown in Table 4, 23 patients (47.9%) showed "disappearance" of the discomforts as a whole. In those whose pre-treatment degree was mild, "disappearance" was as high as 80% of the patients. "Improvement" was seen in 39.6% as a whole, but the improvement was dominant in those whose pre-treatment degree was moderate and severe, namely, more than 50% of the patients in those groups showed "improvement". "No change" was seen in 12.5% as a whole, and in patients whose pre-treatment degree was mild 20.0% of such patients showed "no change" even after treatment.

Table 4: Post-treatment evaluation of discomfort score

Pre-treatment degree (n)	Disappearance		Improvement		No change		Total (n)
	n	%	n	%	n	%	
Mild (15)	12	80.0	-	-	3	20.0	15
Moderate (20)	6	30.0	11	55.0	3	15.0	20
Severe (13)	5	38.5	8	61.5	-	-	13
Total (48)	23	47.9	19	39.6	6	12.5	48

The change in the discomfort score is shown in Table 5. The mean pre-treatment score of 48 patients (excluding the 2 who had no pre-treatment symptom) was 5.2± 2.8 points (varying 0-10) but, after treatment with ActiGel, the mean score significantly decreased ($p<0.001$) to 1.4±1.9 (varying 0-7). No one showed an increase in the post-treatment score compared with the pre-treatment score.

Table 5: Change in the mean discomfort score

	n	Mean	SD	P value
Pre-treatment	48	5.2	2.8	P<0.001
Post-treatment	48	1.4	1.9	

Figure 1 shows the symptom-by-symptom changes in the number of the patients with vaginal discomforts between pre- and post-treatment. The biggest change was seen in “itching”; before treatment 39 patients (81.3%) complained of this symptom but, after treatment, this number had decreased to 18 (37.5%) and this decrease was statistically significant ($p<0.001$). For “vaginal discharge”, the number of complainers decreased from 27 patients (56.3%) to 14 (29.2%); for “malodor”, from 15 (31.3%) to 3 (6.3%); for “vaginal dryness”, from 11 (22.9%) to 3 (6.3%), and for a feeling of “pain” like a burning feeling, from 9 (18.8%) to 1 (2.1%). These decreases were also statistically significant ($p<0.05$, 0.01, 0.05 and 0.05, respectively).

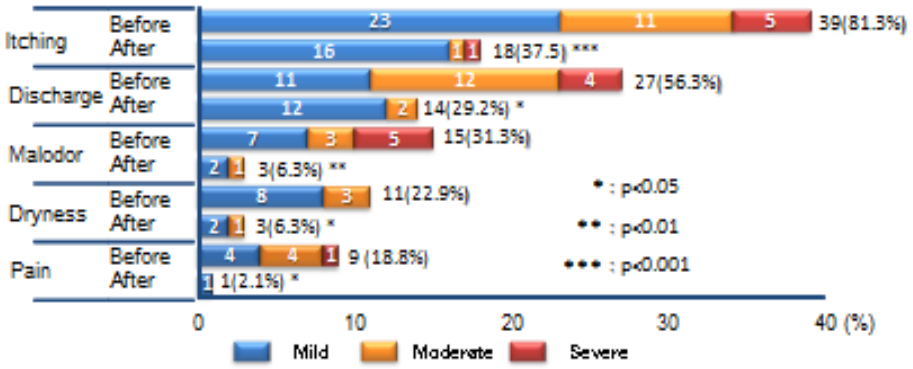

Fig. 1: Symptom-by-symptom change in the No. of patients with vaginal discomforts

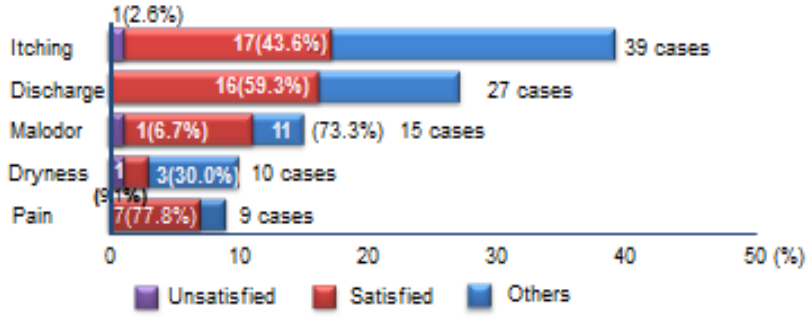

Fig. 2: Symptom-by-symptom satisfaction (patient's self-rating)

Table 6 shows the symptom-by-symptom change in the mean discomfort score. Also here, significant decreases were observed in the mean scores for each of the 5 symptoms such as itching, vaginal discharge, malodor, vaginal dryness and a feeling of pain.

Table 6: Symptom-by-symptom change in the mean discomfort score

Symptoms	Timing	n	Mean	SD	P value
Itching	Before	44	1.5	0.8	P<0.001
	After	44	0.5	0.7	
Vaginal discharge	Before	40	1.2	1.0	P<0.001
	After	40	0.4	0.6	
Malodor	Before	35	0.8	1.1	P<0.001
	After	35	0.1	0.4	
Vaginal dryness	Before	29	0.5	0.7	P<0.05
	After	29	0.1	0.4	
Feeling of pain	Before	31	0.48	0.85	P<0.01
	After	31	0.03	0.18	

Pre- and post-treatment vaginal pH values were obtained from 9 patients. The pre-treatment values varied between pH 5 - 7 (mean: 6.2±0.6) being greater than the normal value. After treatment, the mean pH value significantly decrease ($p<0.001$) to 4.7±0.4 (Table 7).

Table 7: Change in vaginal pH value

Timing	n	Mean	SD	P value
Before	9	6.2	0.6	P<0.001
After	9	4.7	0.4	

5. Users' satisfaction and comment on usability

The symptom-by-symptom users' satisfaction is shown in Figure 2 as expressed by the number of patients and the percentage although not all patients commented. For "itching", out of 39 patients who had complained of this symptom, 38 women (97.4%) made some comment and 17 women (43.6%) were "satisfied" or "quite satisfied". The other one patient was "unsatisfied" because her initial degree of the discomfort was "severe" and the severity was "no change" after treatment. For "vaginal discharge", out of 27 patients suffering from this symptom, 27 women (92.6%) made some comment and 16 women (59.3%) were "satisfied"; no one was "unsatisfied". For "malodor", out of 15 patients who made some comment, 11 women (73.3%) were "satisfied" and only one woman was "unsatisfied" because the change in her discomfort was not so radical, say, from "severe" to "moderate". For "vaginal dryness", out of 11 patients suffering from this discomfort, 10 women (90.9%) made some comment and only 3 women (30.0%) were "satisfied". One woman was "unsatisfied" because the degree of her severity i.e. "moderate" remained unchanged after treatment. For "feeling of "pain", 9 women made some comment and 7 women (77.8%) were "satisfied".

As can be seen from these self-rating results, the satisfaction level was higher in "feeling of pain", "malodor" and "vaginal discharge" in this order, but the satisfaction level was lower than 50% in "itching" and "vaginal dryness".

With regards to "a comfortable feeling" after application of the gel, 38 patients

made some comments. Out of the 38, 12 women (31.6%) assessed to be “comfortable”. For other comments on the usability, 3 women said “I felt stabbing pains”, 5 said “the gel is sticky” and 2 said “it is difficult to apply”.

6. Adverse effects

No adverse effect was observed in any cases. In one patient who did not have “itching” before treatment, “mild itching” was observed after treatment. In another patient, the pre-treatment degree of “vaginal discharge” was “mild” but it turned to “moderate” after treatment. This patient had recurrent candida vaginitis and chlamydial cervicitis concomitantly. She was suffering from severe malodor but, after treatment, she was happy because the malodor had disappeared.

Concerning the usability of ActiGel, the following opinions and comments were brought by the patients:

1) I have feelings of resistance toward using the applicator for 2 weeks. This product is not for a quick therapy, so it is skeptical whether people would use it unless their use-purpose is a temporary cure.
2) It was difficult to insert the gel deeply into the vagina. I had a comfortable feeling when the gel was applied, but such comfortable feeling did not continue long. On days when I feel that the symptom (itching) is rather severe, the symptom occurs again after a while even if the gel is applied. Because it is not so easy to apply the gel a few times a day, an easier way to apply is preferred.
3) The comfortable feeling is short-lived. A smaller sized product will be more convenient to use when women are away from home.
4) I felt a transient slight pain when the gel was applied. After application, vaginal discharge became loose and fluidized. So, a panty-liner was needed.
5) The gel adhered to the panty.
6) After a while, the affected area became dry and I felt itching.
7) After application, I felt hot for a few minutes.
8) The gel came out of the vagina.
9) It is not easy to use the applicator, so I used a finger, instead, for application (2 women)

7. Discussion

According to a survey on 1,200 women in their 20s to 40s conducted in 2010 by Kobayashi Pharmaceutical Co., Ltd., more than 60% of the women had some troubles in their intimate area (pubic region). It is reported that the major trouble was “itching” and the cause was “vaginal discharge”[6]. It is considered that many women are suffering from such troubles and agonizing alone about what to do because they are prone to hesitate to visit a gynecological clinic.

Such troubles come mainly from hormonal changes and imbalances due to environmental changes such as stress. It is pointed out that, under such a condition, lactic acid bacilli (Dodorlein bacilli) decrease and hence the vaginal self-purification effect is reduced favoring the overgrowth of aerobes and/or anaerobic Bacteroides species and Mobiluncus species, thus, leading to inflammatory symptoms as polymicrobial infection. Such symptoms are diagnosed as non-specific vaginitis or bacterial vaginosis. It sometimes induces infectious diseases such as Candida, Trichomonas, Neisseria gonorrhoeae, etc. [1),2),4)]. It is important to offer proper treatment before such secondary infection occurs.

The symptoms of vaginal discomfort can be regarded as a warning signal of genital infection. The front-line prevention of genital infection is indispensable for women’s health care, and gynecologists are requested to draw women’s attention to the importance of proper care of the intimate area (vaginal flora care).

Under these circumstances, we had an opportunity to clinically test Multi-Gyn™ ActiGel developed by BioClin, The Netherlands, which is an acidic vaginal gel based on a high molecular, multi-branched polysaccharide complex (2QR-complex) derived from the parenchyma of Aloe Vera, being encouraged by a clinical report[5)] which demonstrates that ActiGel balances the vaginal flora, acidifies abnormal vaginal pH and serves to improvement of vaginal discomforts.

Out of the 50 patients participated in the study, 41 (82.0%) had a history of vaginal discomforts. Out of the 41 patients, a history of candida vaginosis was seen in 34% and bacterial vaginosis in 24%. Chronic recurrence (> 6 times a year) was also included in the 41 patients. As far as candida-recurrence is concerned, the percentage of women was as high as 38.5% suggesting the seriousness of vaginal discomforts due to candida-infection.

Before treatment with ActiGel, the vaginal discomforts were scored into 10 points (from 0 for "none" up to 10 for "quite severe") and, according to the scores assessed, grouped into 4 degrees "none", "mild", "moderate" and "severe". And, 70% of the patients were included in either "mild" or "moderate" groups suggesting that the majority is in the pre-severe degrees. The mean discomfort score was 5.2±2.8 points (excluding the 2 cases without pre-treatment discomfort symptom) also suggesting that the majority is in the "moderate" or "mild" groups before treatment.

For specific discomforts, "itching" was seen in 81.3% of the patients, "vaginal discharge" in 56.3% and "malodor" in 31.3", suggesting that the majority was suffering from itching and discharge. This was considered to be in consistent with the most reported vaginal discomforts that women are suffering from.

At the first visit, the participants were instructed to apply the gel once or twice a day depending on the symptoms and, at the next visit, they were interviewed to assess the results and effects. As a result, 87.5% of the patients showed "disappearance" or "improvement" of the symptoms and only 12.5% showed "no change". The "no change" was not seen in the "severe" group but seen in the "moderate" and "mild" groups at the rate of 15.5% and 20.0%, respectively. This indicates that the efficacy was predominantly observed in the higher discomfort score groups.

As for the symptom-by-symptom change in the number of patients, significant decreases of the number of patients were seen in each complaint of "itching",

“vaginal discharge”, “malodor”, etc. after treatment. However, “itching” still persisted in 18 patients (37.5%) consisting of 16 in the “mild” group and 1 each in the “moderate” and “severe” groups. Also “vaginal discharge” still persisted in 14 patients (31.3%) consisting of 12 in the “mild” group and 2 in the “moderate” group. From these results it was considered that ActiGel would play an auxiliary role, not a role of a direct therapeutic agent.

As for the patient’s self-rating satisfaction upon use, the level of satisfaction for “itching” was 43.6% that is lower than that for “vaginal discharge” (59.3%) and “malodor” (73.3%). Thus, also here, the efficacy of ActiGel was considered to be present through the intermediary of the flora environment rather than a rapid-acting effect.

The mean vaginal pH values in 9 patients decreased from 6.2±0.6 to 4.7±0.4. In consideration of this pH change and the above-mentioned changes in the symptoms, the improvement of vaginal discomforts was considered to have been presented by re-balancing of vaginal flora and recovery of vaginal self-purification effects.

Concomitant use of antimycotics or antimicrobials was practiced in 9 out of the 48 patients. It is supposed that ActiGel would not interfere with these drugs but produce a synergetic effect. However, this point needs to be studied in more detail in the future.

In addition, as commented by the patients, women seem to have a resistance towards the continuous use of the attached applicator and they have difficulty in actually using it. So, improvement of the way of application (insertion) will be necessary. Another complaint about the product is that the gel came out of the vagina to the vulva after being inserted, and made a panty dirty. That may be because one cannot correctly quantify a dose (one-time insertion volume) or because the volume was too much. Therefore, it will be necessary to improve the explanatory note about the insertion method.

Conclusion

From these findings, ActiGel is considered effective in women suffering from vaginal discomforts. In particular, satisfactory effects were observed on “itching”, “vaginal discharge” and “malodor” being the symptoms that many women suffer from. This efficacy on BV-related complaints was also supported by the vaginal pH data obtained from 9 patients.

As can be seen from the users’ comments on satisfaction of the application of ActiGel, just 31.6% were happy and some complaints were pointed out, for example, “it is too sticky or gooey to be applied” and “it comes out to the vulva and makes a panty dirty”. In addition, improvement of the applicator was considered to be homework to be solved in future.

ActiGel was useful for women complaining of vaginal discomforts, and it was also useful as a supportive cure to the drugs for the underlying diseases such as bacterial vaginosis (non-specific vaginitis) and candida vaginitis.

The present study is a preliminary and exploratory study and, therefore, a further detailed study is preferable.

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