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ANTIBIOTIC AND EJACULATION TREATMENTS IMPROVE RESOLUTION RATE OF LEUKOCYTOSPERMIA IN INFERTILE MEN WITH PROSTATITIS

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ABSTRACT

Leukocytospermia has been associated with notable adverse effects on semen parameters and sperm function. The present study was undertaken to identify men with leukocytospermia and prostatitis in an infertility population and assess the effects of various treatments. One million white blood cells (WBC)/ml semen was defined as leukocytospermia. An expressed prostatic fluid was analyzed for the presence of white blood cells. The presence of more than 10 WBCs/high power field on expressed prostatic secretion was needed for the diagnosis of prostatitis. Those men who had more than one million WBCs in their semen and more than 10 WBCs/high power field on expressed prostatic secretion were enrolled in this study. Of two hundred sixty-three men screened for the presence of leukocytospermia and prostatitis, forty-eight men met both criteria. They were blindly and randomly assigned to one of three groups. Group 1 received no treatment. Group 2 were treated with trimethoprim 80 mg-sulfamethoxazole 400 mg (TMP-SMX) orally twice per day for one month. Group 3 were treated not only with the same antibiotic regimen as group 2 but also were instructed to ejaculate frequently (at least once every three days) for one month. Significant resolution of leukocytospermia occurred in the order of patient groups $3 > 2 > 1$ at one month. The resolution rate of leukocytospermia of each group was 76% in group 3, 56% in group 2 and 6.7% in group 1. The rates in groups 2 and 3 were significantly higher than that in group 1 ($p < 0.05$). The resolution was sustained at two and three months in both groups 2 and 3, and a higher rate of resolution was obtained in group 3. We conclude that antibiotic with frequent ejaculation effectively treats leukocytospermia.

Key Words: Leukocytospermia, Infertility, Prostatitis

INTRODUCTION

In 40% of infertile couples, a male factor is implicated for which the cause is often unknown.[1] Acute and chronic infections of the genitourinary tract may play a contributing role in male factor infertility. An infectious process may impair fertility by adversely affecting sperm function, resulting in testicular damage or causing obstruction of the genital tract.[2] An elevated seminal leukocyte count may reflect a genital tract infection and has been observed to be associated with male infertility. Men with leukocytospermia were found to have significant decreases in total sperm number, total motile sperm, and sperm velocity.[3] White blood cells (WBCs) have been shown to affect fertilization adversely in the hamster sperm penetration assay (SPA).[4,5] Van der Verr et al.[6] and Cohen et al.[7] have reported that the fertilization rate in human in vitro fertilization is reduced when numbers of leukocytes are increased in semen.

Conventionally, the presence of increased numbers of leukocytes has been regarded as a clinical sign of genital tract infection. However, leukocytospermia has a heterogeneous etiology,

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consisting of infection, inflammation and autoimmunity.[8] Therefore, we identify men with leukocytospermia and prostatitis using the method described by Meales and Stamey.[9] Berger et al.[10] showed that half of infertile men with abnormal SPAs and increased number of leukocytes treated with doxycycline had normal SPA results and improved pregnancy rates after treatment. The aims of the present study are [1] to identify the men with leukocytospermia and prostatitis in an infertility population; [2] to evaluate the effectiveness of antibiotic treatment with frequent ejaculation in the men with leukocytospermia; and [3] to assess the time course of treatment of leukocytospermia.

MATERIALS AND METHODS

The study was conducted on men who consecutively attended an Andrology Clinic of the Nagoya University Hospital with chief complaint of infertility between January 1991 and October 1994. They were investigated to determine the existence of leukocytospermia. This evaluation consisted of taking the history, physical examination and analyses of expressed prostatic secretion and semen. One million WBCs/ml semen was defined as leukocytospermia. An expressed prostatic fluid was analyzed for the presence of WBCs. The presence of more than 10 WBCs per high power field on expressed prostatic secretion (EPS) was needed for the diagnosis of prostatitis. A bacterial organism was considered to be localized in the prostate if there was at least a 10-fold increase in CFU (colony forming unit) per milliliter between the first-void urine (VBl) specimen and the post-prostatic massage urine (VB3) specimen or the EPS if the VB3 specimen did not meet this criterion.[9] Those men who had more than one million WBCs in their semen and more than 10 WBCs/high power field on EPS were enrolled in this study. Semen cultures were not performed on any of the men.

Of two hundred sixty-three men screened for the presence of leukocytospermia and prostatitis forty-eight men met both criteria. They were randomized into the treatment protocol and were blindly assigned to one of three groups. Group 1 (n=15) received no treatment. Group 2 (n=16) were treated with trimethoprim 80 mg, sulfamethoxazole 400 mg (TMP-SMX) orally twice per day for one month. Group 3 (n=17) were treated not only with the same antibiotic regimen as group 2 but also were instructed to ejaculate frequently (at least once every three days) for one month.

They were followed at monthly intervals for three months with repeated analyses of semen for the presence of leukocytes. Repeated monthly prostatic massages were not performed because of difficulty with patient compliance. Resolution of the leukocytospermia was achieved if the leukocyte concentration was less than one million/mL. Comparison among the three groups at each monthly time interval was analyzed using chi-square analysis.

RESULTS

Of the 263 men screened for leukocytospermia, 48 (18.3%) met both criteria for diagnosis of leukocytospermia and prostatitis used in the present study. The treatment groups did not differ greatly with respect to age, sperm concentration, motility, or percent of normal sperm morphology. The average age of patients was 35.4 years, with an average sperm concentration of 12.5×10^6/ml; motility, 35%; and normal morphology, 68.2%. None of the men initially were seen specifically for any genitourinary complaints, but 35% had pollakisuria, 21% had nocturia, and 13% had pain with ejaculation on review of systems. Isolated bacteria from urine after

prostatic massage included seven strains of *Escherichia coli*: group 1 (1 strain), group 2 (3 strains), and group 3 (3 strains); two strains of *Enterobacter cloacae*: group 2 (1 strain) and group 3 (1 strain); and one strain of *Pseudomonas aeruginosa* in group 3. Tests for detection of *Chlamydia trachomatis* and *Mycoplasma* spp. were not performed. No relationship between bacterial culture results and leukocyte levels was found. The frequency of ejaculation of the patients before starting the study was 5 ± 1.3 /month (range, 2 to 10 times/month). The patients in group 3 increased their frequency from 5 times/month to 10 times/month during the 1-month treatment phase. At one month after treatment, 1 patient (6.7%) in group 1, 9 (56%) in group 2, and 13 (76%) in group 3 had their leukocytospermia resolved. Both group 2 and group 3 showed significant improvement in resolution of leukocytospermia by chi-square analysis compared with group 1 ($p < 0.05$ and $p < 0.01$, respectively). These results are summarized in Table 1.

The effectiveness of treatment was sustained at two and three months follow-up in groups 2 and 3. At two months, 5 (36%) of the patients in group 2 and 11 (79%) in group 3 continued to have resolution of their leukocytospermia compared with 0 (0%) in group 1. Similar results were observed at three months follow-up. Group 2 and group 3 had 5 (36%) and 10 (71%) men with significant resolution of leukocytospermia, respectively, compared with 0 (0%) in group 1 ($p < 0.05$). There was no significant difference in the resolution rate of leukocytospermia between group 2 and group 3. These results are summarized in Table 2. Six pregnancies occurred during the three months of the study. One pregnancy occurred in group 1, two in group 2, and three in group 3. Five of these pregnancies occurred in the patients who responded to the treatment. The only pregnancy in group 1 occurred in a patient who spontaneously resolved his leukocytospermia. The number of pregnancies was too small to make statistically meaningful comparisons between the groups.

Table 1. Efficacy of Treatment at One Month after Starting Various Treatments

Treatment group[c]	No. of patients	Resolution of leukocytospermia[a]	p value
1	15	1 (6.7%)	
2	16	9 (56%)[b]	<0.05
3	17	13 (76%)[b]	<0.01

[a] Values in parentheses are percentages.

[b] Significant differences when compared by chi-square analysis with the no-treatment group.

[c] Group 1: no treatment, group 2: antibiotic alone, group 3: antibiotic and frequent ejaculation.

Table 2. Efficacy of Treatment at Two and Three Months after Starting Various Treatments

		Resolution of leukocytospermia	
Treatment group[c]	No. of patients	2 months[a]	3 months[a]
1	14	0 (0%)	0 (0%)
2	14	5 (36%)[b]	5 (36%)[b]
3	14	11 (79%)[b]	10 (71%)[b]

[a] Values in parentheses are percentages.

[b] Significant differences ($p < 0.05$) when compared by chi-square analysis with the no-treatment group.

[c] Group 1: no treatment, group 2: antibiotic alone, group 3: antibiotic and frequent ejaculation.

DISCUSSION

In the present study a strict diagnostic definition of leukocytospermia and prostatitis was employed to evaluate the efficacy of various treatments for asymptomatic infertile men with leukocytospermia. At one month follow-up both groups 2 and 3 revealed significant improvement in resolution of leukocytospermia compared with group 1. This was maintained at two and three months follow-up in groups 2 and 3. The resolution rates at two and three months follow-up were 36% and 36%, respectively, in group 2, and 79% and 71%, respectively, in group 3. All of the pregnancies were achieved by the patients who had resolution of their leukocytospermia.

Several reports have demonstrated that leukocytes can affect seminal quality and fertility.[3-5] Wolf et al[4] have reported increased total leukocytes in the semen in men with infertility, and noted an adverse effect of leukocytospermia on sperm concentration, velocity, and motility. Interestingly, in their report, no relationship between bacterial culture results and leukocyte levels was found, suggesting that the isolation of bacteria in semen may not always indicate an inflammatory process and that the significance of their presence is uncertain. Berger et al[11] reported that the strongest correlation with an abnormal sperm penetration assay was the increased presence of leukocytes in semen; in our results, too, no correlation between semen bacterial culture results and sperm penetration scores was noted. In the present study we also confirmed that there was no relationship between bacterial culture results and leukocyte levels. Although likely *Chlamydia trachomatis* infections or *Mycoplasma* spp. infections can not be excluded, these results suggest that there were patients with either bacterial or non-bacterial prostatitis having leukocytospermia. Maruyama et al[5] have shown that hamster egg penetration rates were decreased when leukocytes from fertile donors were added to sperm suspensions. In their analyses of factors affecting in vitro fertilization outcomes, Cohen et al[8] and Talbert et al[12] found that the semen parameters that correlated most significantly with a reduced ability to fertilize oocytes were a slow rate of forward progression of sperm and an elevated number of leukocytes in semen. In this study leukocytospermia was used as a marker to identify those men who are most likely to benefit from antibiotic treatment.

Resolution of leukocytospermia with antibiotics implies an infectious etiology. However, leukocytospermia can be attributed to heterogeneous causes other than *Chlamydia trachomatis* infections or *Mycoplasma* spp. infections of the prostate gland. The increased number of WBCs in semen may reflect a genital tract infection or may be secondary in an immunologically dynamic tissue capable of initiating both humoral and cell-mediated immune responses. For this reason antibiotics and frequent ejaculation were used alone and in combination in this study. Frequent ejaculation was used to clear the prostate gland and seminal vesicle of their stored secretions. This may allow antibiotics to work more effectively. TMP-SMX was chosen because of its broad spectrum of antibiotic activity and good penetration into the prostate.

In addition to sperm, semen contains round cells comprising leukocytes and immature germ cells. However, with conventional staining techniques it is occasionally difficult to differentiate morphologically between these two round-cell populations. Monoclonal antibodies directed against leukocyte antigens can provide a useful diagnostic tool to identify leukocytes in the semen. However, immunohistochemical methods are expensive and time consuming on a routine basis and are used primarily for research purposes. The EPS (expressed prostatic secretion) provides further evidence of increased leukocytes in the male accessory glands. Identification of WBCs in the semen and EPS was used in combination in this study to identify more accurately men with leukocytospermia due to infectious etiology.

In conclusion, leukocytospermia and prostatitis were relatively frequent findings in infertile men without any initial genitourinary complaints. Leukocytospermia can be treated effectively

with antibiotics and frequent ejaculation. Further studies concerning the role of leukocytes in the male reproductive tract will offer clinically important information.

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