THE EFFECTS OF LOW-DOSE ASPIRIN TREATMENT IN OVARIAN AND UTERINE RESPONSIVENESS, IMPLANTATION AND PREGNANCY RATES IN PATIENTS UNDERGOING ICSI

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Abstract- Vascularization of the follicle may play a role in its maturation and aspirin seems to increase this vascularization. In this investigation we have studied the effects of low-dose aspirin on ovarian and uterine response, implantation and pregnancy rates in patients undergoing intracytoplasmic sperm injection (ICSI). This prospective semirandomized, double-blind, placebo-controlled study was undertaken in Mirza Kouchek Khan IVF center. Forty four infertile patients who were undergoing ICSI cycle were studied and they were divided in two groups. The mean age of patients and distribution of the cause of infertility in two groups were similar. In the treatment group, 22 patients underwent controlled ovarian hyperstimulation and received a daily dose of 100 mg aspirin. In the control group 22 patients underwent controlled ovarian hyperstimulation in association with placebo. Number of follicles ≥ 15mm in diameter, number of oocytes retrieved, endometrial thickness, cancellation rate, number of transferred embryos and implantation and pregnancy rates were analyzed in two groups. There was no statistically significant difference between the treatment and control groups for each of the above variables (P > 0.05). This study showed that low dose aspirin therapy has no added effect to ovarian and uterine response, implantation and pregnancy rates in ICSI patients. Further studies are recommended for confirmation of our results.


Key words: Aspirin, ICSI- ET, pregnancy rate

INTRODUCTION

Aspirin is a salicylate non-steroidal anti-inflammatory drug (NSAID). Aspirin and other salicylates have analgesic, antiinflammatory and antipyretic properties (1). They act as inhibitors of the enzyme cyclooxygenase (2), which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. Aspirin also inhibits platelet aggregation while non-acetylated salicylate do not (1). Aspirin’s antiplatelet activity has led to its use in a variety of disorders such as unstable angina, ischemic stroke and anti phospholipid antibody syndrome (1). Aspirin has also been tried in pregnancy-induced hypertension for the prevention of pre-eclampsia and intra-uterine growth retardation (1,3-5). Vascularization of the follicle may play a role in its maturation from the early follicular phase. Aspirin seems to increase this vascularization because of a vasodilatation effect, therefore, it may improve ovarian and uterine responsiveness. This study was undertaken to determine the effects of low-dose aspirin treatment in infertile patients who were undergoing intracytoplasmic sperm injection (ICSI) cycles.

MATERIALS AND METHODS

This was a prospective semirandomized, double-blind, placebo-controlled study. Randomization was performed by “every other subject” method and each patient received her medication through a third person. Both patients and clinical staff were blinded to treatment. We studied 53 patients whose infertility was due to a tubal factor or male factor other than azospermia or oligoasthenoteratospermia, because
Azospermic patients were a limitation for ICSI so they were excluded from the study. The 53 patients were randomly divided into treatment and control groups. All patients were informed and a consent form was taken according to Helsinki protocol. The treatment group (27 patients) received a daily oral dose of 100 mg of aspirin and the control group (26 patients) received placebo. Both groups started aspirin or placebo co-treatment on the 21st day of their preceding menstrual cycle. Controlled ovarian hyperstimulation was initiated in all patients with the gonadotropine releasing hormone (GnRH) analogue, busereline, started in the midluteal phase (21st day) of the previous cycle with a dose of 0.5 mg/day and decreased to 0.3mg/day from 2nd day of menstrual cycle. Then gonadotropin therapy was given using HMG 3 ampules per day for all patients. GnRH analogue injection was continued up to and including the day of HCG administration and cycle monitoring was performed with serial transvaginal ultrasonography.

For minimizing the measurement bias all scans and measurements were performed by the same operator. Transvaginal follicular aspiration and ICSI embryo transper (ET) were performed after our standard protocol. Pregnancy was detected by increasing serum β-HCG level in at least two determinations (12-14 days after ET) and was confirmed by sonographic screening of the gestational sac one week after the last β-HCG determination. Pregnant patients continued the medication which included aspirin or placebo co-treatment through 12 week’s gestation.

For minimizing the confounding variables, all of the following patients were excluded from the study:

1. All the patients with any known ovulatory dysfunction (such as abnormal menstrual pattern, abnormal hormonal pattern and previous unilateral oophorectomy).
2. All the patients who required TESE (testicular sperm extraction) or PESA. (percutanus epandymal sperm aspiration).
3. All the patients whose treatment protocol fell in a pattern other than our standard protocol (e.g., the patients who needed in increase or decrease in the dose of gonadotropines during follow up or those who received larger dose of busereline during treatment cycle.

All the patients received the same protocol of induction of ovulation. The ovarian and uterine responsiveness and IVF outcome variables were analyzed, including number of follicles ≥ 15 mm, cancellation rate, endometrial thickness on the day of HCG administration, number of oocytes retrieved, number of transferred embryos, implantation and pregnancy rates. The data were analyzed with the use of the two-tailed students’s t-test, Mannwhitney test and Chi-square test. P<0.05 was considered statistically significant.

**RESULTS**

The 53 patients were randomly divided into treatment (27 patients) and control groups (26 patients). Five patients in treatment group were excluded from study , one became pregnant spontaneously during GnRH therapy, two due to cyst formation on GnRH therapy and two due to unresponsiveness of ovaries to gonadotropines. Four patients in control group were excluded from study, one due to inability of her husband to give semen sample, one due to cyst formation on suprefact therapy, and two due to ovarian unresponsiveness to gonadotropines. At last 22 patients in each group were analyzed. The results of this study are summarized in tables 1 and 2. The mean (±SD) age was similar in the treatment and control groups (28.41±4.34 versus 28.27±3.45, respectively); all the patients were under age 35.

The cause of infertility was similar in the treatment and control groups (54.5% male factor, 40.9% tubal factor and 4.5% both factors versus 54.5% male factor, 31.8% tubal factor and 13.6% both factors, respectively).

The cancellation rate due to cyst formation or unresponsiveness of ovaries was similar in treatment and control groups (0.18% versus 0.13%, respectively). Ovarian responsiveness was expressed as the number of follicles ≥ 15mm on the day of HCG administration and the number of oocytes retrieved. The mean (±SD) number of follicles ≥ 15 mm on the day of HCG administration was 6.82±3.69 versus 5.86±1.96 for the treatment and control groups, respectively (P>0.05). The mean (±SD) number of oocyte retrieved was 5.18±3.84 versus 4.73±2.62 for the treatment and control groups, respectively (P<0.05). The mean (±SD) thickness of endometrium as a marker for endometrial responsiveness, on the day of HCG administration was 9.61±3.18 versus 10.17±2.15 for the treatment and control groups respectively (P>0.005). The mean (±SD) number of transferred embryos was 2.45±2.06 versus 2.36±1.40 in treatment and control groups, respectively (P>0.05).
Table 1. ICSI- ET outcome in the treatment and control groups*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th>Control group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>28.41±4.34</td>
<td>28.27±3.45</td>
<td>NS</td>
</tr>
<tr>
<td>Cancellation rate(%)</td>
<td>0.18</td>
<td>0.13</td>
<td>NS</td>
</tr>
<tr>
<td>No. of follicles</td>
<td>6.82±3.69</td>
<td>5.86±1.96</td>
<td>NS</td>
</tr>
<tr>
<td>End. thickness(mm)</td>
<td>9.61±3.18</td>
<td>10.17±2.15</td>
<td>NS</td>
</tr>
<tr>
<td>No. of oocytes</td>
<td>5.18±3.84</td>
<td>4.73±2.62</td>
<td>NS</td>
</tr>
<tr>
<td>No. of embryos</td>
<td>2.45±2.06</td>
<td>2.36±1.40</td>
<td>NS</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>13.63</td>
<td>27.24</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical PR (%)</td>
<td>13.63</td>
<td>27.27</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant; PR, Pregnancy rate; End, endometrium

*Data are given as means ± SD except for cancellation, implantation and clinical pregnancy rates.

Table 2. Causes of infertility in the treatment and control groups*

<table>
<thead>
<tr>
<th>Cause of Infertility</th>
<th>Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>Male factor</td>
<td>12</td>
<td>54.5</td>
</tr>
<tr>
<td>Tubal factor</td>
<td>9</td>
<td>40.9</td>
</tr>
<tr>
<td>Both factors</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>100</td>
</tr>
</tbody>
</table>

*P value > 0.05

The implantation and clinical pregnancy rates were 13.63% (3 cases) versus 27.27% (6 cases) for the treatment and control groups, respectively. The difference was not statistically significant (P=0.076).

No side effect was observed in patients treated with aspirin; GI symptoms or other types of symptoms and bleeding during aspiration were similar in both groups.

DISCUSSION

Aspirin has several pharmacologic properties. It is an inhibitor of the enzyme cyclooxygenase. In blood platelets this enzyme prevents the synthesis of thromboxane, a compound which is a vasoconstrictor, causes platelet aggregation and is thus potentially thrombolic (1). When this enzyme is irreversibly inhibited by low dose aspirin treatment, platelet aggregation and vasoconstriction may be avoided which in turn may improve folliculogenesis and implantation (6,7). In blood vessel walls, the enzyme inhibition prevents the synthesis of prostacyclin (6,8,9) which is a vasodilator and has antithrombotic properties and is thus potentially paradoxical. The duration of these effects, however, may be somewhat different, with the effect on the vascular tissue generally being short lived compared to the effect on platelets. The different duration of effects may be explained by the fact that vascular cells regain the ability to regenerate prostacycline in a few hours but platelets are unable to resynthesize cyclooxygenase thus resulting in no new thromboxane synthesis being produced until after about 24hr (1) and/or even more longer for total life span of platelet, 8-11 days (7,10,12). Aspirin therefore appears to have paradoxical biological effects, both antithrombotic and thrombogenic. The thrombogenic effect occurs only with high doses because platelet cyclooxygenase is more selective than vascular cyclooxygenase therefore low dose aspirin inhibits synthesis of TXA2 without affecting the excretions of PGI2 (13-15) thus increasing the increase in blood flow velocity in the uterine and ovarian arteries. PGI2 has been proposed to modulate the relaxation of vascular smooth muscle of endometrial vessels. As low dose aspirin treatment shifts local production of TXA2 toward PGI2, it may improve implantation because of its effect on the endometrium.

Vascularization of the follicle may play a role in its maturation from the early follicular phase. Aspirin seems to increase this vascularization because of a vasodilator effect that could result in preferential delivery of gonadotropin hormones or other growth substances required for steroidogenesis. This may improve folliculogenesis and increase the number of oocytes retrieved. While considering the above explanation it seems logical to use low doses of aspirin as a drug that may improve ovarian and uterine responsiveness as studies performed by Wada et al. (16) and Rubinstein et al. (17), both revealing that aspirin significantly improves ovarian and uterine responsiveness in patients undergoing IVF. The Rubinstein study although was a large RCT but suffers from the effects of some important confounding variables such as nonadjustment of gonadotropin and GnRH agonist dose and the advanced age of the patients. For comparative purposes we performed this placebo-controlled clinical trial but we found no relation between aspirin therapy and improvement in ovarian and uterine responsiveness, implantation and pregnancy. One of the strongest point of our study was its high internal validity. All confounding variables and measurement biases were decreased as low as possible but the
The sample size was not large enough to show a definite statistical conclusion.

In conclusion, this study demonstrated that low dose aspirin therapy has no beneficial effect in ICSI results. Which could be due to the small sample size of this study so it seems that further studies are required to determine the exact effect of aspirin on ovarian and uterine responsiveness, implantation and pregnancy rates.

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REFERENCES


