

9. Effect of bone marrow mesenchymal stem cells transplantation on BMP-15 expression and Graaflan follicle count in mice model of endometriosis

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ORIGINAL ARTICLE:

Effect of bone marrow mesenchymal stem cells transplantation on BMP-15 expression and Graafian follicle count in mice model of endometriosisRatriana Via Parasti¹, Widjiati², Sri Ratna Dwiningsih^{*1}¹Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr Soetomo Hospital, Surabaya, Indonesia, ²Department of Veterinary Obstetrics, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Objectives: To determine the effect of bone marrow mesenchymal stem cells (BMSCs) on BMP-15 expression and Graafian follicle count in endometriosis mice.

Material and Methods: This study was a laboratory randomized clinical trial on *Mus musculus*. The object of the study was 42 mice which were divided into 3 groups, the control, endometriosis, and endometriosis + BMSCs groups. Comparison of BMP-15 expression and Graafian follicle count between groups was evaluated.

Results: Immunohistochemical analysis showed that BMP-15 expression in control, endometriosis, and endometriosis + BMSCs groups had $p=0.551$, $p=0.446$ and $p=0.917$ with ANOVA test $p=0.273$, indicating no statistically significant differences between groups. Graafian follicular count in the three groups had $p=0.31$, $p=0.001$, and $p=0.006$, with the Kruskal-Wallis test $p=0.001$. Graafian follicles in the endometriosis + BMSCs group were higher than those in control and endometriosis groups.

Conclusion: In the endometriosis mouse model with bone marrow stem cell transplantation the BMP-15 expression in each group did not show a difference, but a significant difference was found in the number of Graafian follicles.

Keywords: Endometriosis; bone marrow stem cells; BMP-15

ABSTRAK

Tujuan: Untuk mengetahui efek BMSCs terhadap ekspresi BMP-15 dan jumlah folikel de Graaf pada mencit model endometriosis.

Bahan dan Metode: Penelitian ini merupakan randomized clinical trial eksperimental laboratorium terhadap *Mus musculus*. Objek penelitian adalah 42 mencit yang dibagi menjadi 3 kelompok, yaitu kontrol, endometriosis, dan endometriosis + kelompok BMSCs. Kemudian, perbandingan ekspresi BMP-15 dan jumlah folikel de Graaf antar kelompok dievaluasi.

Hasil: Analisis imunohistokimia menunjukkan bahwa ekspresi BMP-15 pada kelompok kontrol, endometriosis, dan kelompok endometriosis + BMSCs adalah memiliki $p=0.551$, $p=0.446$ dan $p=0.917$ dengan uji ANOVA $p=0.273$, menunjukkan tidak dapat beda bermakna secara statistik antar kelompok. Jumlah folikel de Graaf pada ketiga kelompok memiliki $p=0.31$, $p=0.001$, dan $p=0.006$, dengan uji Kruskal-Wallis $p=0.001$. Folikel de Graaf pada kelompok endometriosis + BMSCs lebih tinggi daripada pada kelompok kontrol dan endometriosis.

Simpulan: Pada model tikus endometriosis dengan transplantasi sel punca sumsum tulang ekspresi BMP-15 pada tiap kelompok tidak menunjukkan perbedaan, namun perbedaan bermakna didapatkan pada jumlah folikel de Graaf.

Kata kunci: Endometriosis; sel punca sumsum tulang; BMP-15

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INTRODUCTION

Endometriosis is a disorder of the female reproductive system, where the endometrium grows outside the uterus. This condition is most often found in the ovaries and peritoneum, also causing premenstrual pain and dysmenorrhea. The main symptoms in this disease are pelvic pain, dysmenorrhea and dyspareunia. Endometriosis is one of the causes of infertility and is diagnosed in 25-40% of infertile women. Although it can interfere with fertility, the mechanism is still uncertain.¹

Folliculogenesis is the center of female fertility and is formed by communication of the endocrine complex between the central nervous system, the hypothalamus and the ovary. In this case, the intra-ovarium paracrine message is the basis of oocyte maturation, growth and development of follicle, and provides adequate sensitivity for gonadotropin stimulation. Therefore, messages originating from oocytes should be continuous and can assemble a series of formations from the primordial follicles and control the forthcoming maturation of the follicles.² The decreased quality of oocytes may be a consequence of folliculogenesis disorders. A study by Bahtiyar et al. even obtained follicular fluid in endometriosis patients that contained factors that can affect the pattern of endometrial growth in other tissues.³

BMP-15 is a growth and differentiation factor originating from oocytes. This factor is an important regulator in folliculogenesis and granulosa cell activity.² A recent study has shown rapid progress in the concept that oocytes have an important role in regulating the function of surrounding somatic cells. Research by Pasquale et al. identify BMP-15 mutations in women who experience ovarian failure due to ovarian dysgenesis.⁴

Levels of GDF 9 in female follicle endometriosis are found to be lower than in non-endometriosis women.⁵ However, until now there has been no journal that mentions the existence of an association between BMP-15 expression levels and endometriosis. Endometriosis is also said to increase granulosa cell apoptosis so that it can affect the process of folliculogenesis and steroidogenesis.⁶

Stem cells are a source of cells that can renew themselves for a long time. Because it has the ability to become various types of cell, stem cells can be used for regenerative therapy in diseases caused by cell damage.^{7,8} This study assumes that the administration of bone marrow mesenchymal stem cells can reduce granulosa cell apoptosis and increase BMP-15 expression so that paracrine communication between granu-

losa cells and oocytes is improved, thereby it can hold a folliculogenesis process.

This study observed the BMP-15 expression as an indicator of oocyte quality in endometriosis because studies using GDF 9, which is a homologous sequence of BMP-15 as an oocyte quality profile of endometriosis, had been carried out. This study aims to analyze differences in BMP-15 expression in endometriosis models as an indicator of oocyte quality after the administration of mesenchymal bone marrow stem cells.

MATERIALS AND METHODS

This study was a laboratory experimental study in mice using randomized double blind design. This study was conducted in August 2017 to September 2017 in in vitro Embryology Laboratory, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia. Study sample comprised 42 female mice (*Mus musculus*) that had met the inclusion criteria, aged 3 months, weight 20-40 g.

The subjects were divided into three groups randomly. The first group (K0), as a control, injected with 0.9% NaCl intraperitoneally. The second group (K1) was a group of mice with endometriosis models who were given intramuscular (IM) injections of cyclosporine A and estrogen, then intraperitoneal (IP) injection was given. Three days later this group received the second estrogen injection, then eight days later received a MEM buffer injection intravenously (IV). The third group (K2) was a group of mice with endometriosis models who obtained injections of cyclosporine A and estrogen injections intramuscularly (IM), then intraperitoneal (IP) endometrial injection. Eleven days after the administration of endometrium this group received a transplant of 2×10^7 bone marrow mesenchymal stem cells intravenously (IV). All three groups were given ovarian stimulation with PMSG and hCG and then oocyte harvesting was carried out.

Before determining the type of statistics used, data normality test was conducted to determine the normality of data distribution. In this study, BMP-15 expression data and the number of Graafian follicles obtained from each study group were tested with a normality test with a significance level of $p > 0.05$. If the distribution was normal ($p > 0.05$), the One-Way ANOVA test was carried out because in this study there were more than two groups. If it was abnormally distributed ($p < 0.05$), a non-parametric test was carried out, followed by a post-hoc test. Then, a regression test was performed to see the effect of some variables on other variables.

RESULTS AND DISCUSSION

13 Bone Morphogenetic Protein-15 (BMP-15)

13 Table 1. Mean expression of BMP-15 in the control, endometriosis, and endometriosis + BMSCs groups

	BMP-15
K0 (Control)	1.8±0.8
K1 (Endometriosis)	1.6±1.2
K2 (Endometriosis+BMSCs)	2.1±1.0

Table 1 shows mean BMP-15 expression in each group. The lowest mean BMP-15 was found in the endometriosis group, while the highest mean was found in endometriosis + BMSCs group. In the normality test using Shapiro-Wilk, the degree of significance of the control group, endometriosis, and endometriosis + BMSCs were $p=0.551$, $p=0.446$ and $p = 0.917$. Because the p value in 3 groups was >0.05 , then the distribution of the three groups' data was normal. Because the data were normally distributed, the test was followed with parametric one-way ANOVA test.

Table 2. Comparison of BMP-15 expressions between groups (One-Way ANOVA test)

	n	Mean ± SD	P value
K0(Control)	11	1.8±0.8	0.50
K1(Endometriosis)	11	1.6±1.2	
K2 (Endometriosis+BMSCs)	11	2.1±1.0	

Table 2 shows the comparison of BMP-15 expression using one-way ANOVA test with a value of $p=0.05$, which means that there is no significant difference in BMP-15 expression between groups.

Graafian follicle count

This study compared the number of Graafian follicles between control, endometriosis, and endometriosis + BMSCs groups. The lowest Graafian follicle count was found in the endometriosis group, while the highest mean was obtained in the control group. The normality test using Shapiro-Wilk showed that the three groups had abnormal data distribution ($p < 0.05$), so the test was continued using Kruskal-Wallis test. Table 3 with the Kruskal-Wallis test resulted in a value of $p=0.001$ ($p < 0.05$), it can be concluded that there were at least differences in Graafian follicle count between 2 groups statistically, so that it was followed by Mann-Whitney post-hoc test.

Table 3. Comparison of Graafian follicles count between groups (Kruskal-Wallis test)

	N	Median (Min-Max)	P value
K0 (Control)	14	4(2-9)	0.001
K1 (Endometriosis)	14	1.5(1-5)	
K2 (Endometriosis+BMSCs)	14	3.5(2-8)	

Table 4. Mann-Whitney post-hoc analysis comparing Graafian follicle counts between groups (Kruskal-Wallis test)

	N	Median (Min-Max)	P value
K0 (Control)	14	4(2-9)	0.001
K1 (Endometriosis)	14	1.5(1-5)	
K2 (Endometriosis+BMSCs)	14	3.5(2-8)	

Table 4 shows a significant difference between endometriosis group and endometriosis + BMSCs group, also between control group and endometriosis group. However, no significant differences were found between control group and endometriosis + BMSCs group.

Characteristics of the samples

16 BMP-15 has an important role in the regulation of folliculogenesis and follicular function in the ovary. In vitro studies in mice used recombinant BMP-15 identified granulosa cells as the predominant target cell type 15 BMP in the ovary.⁹ The presence of intravarian paracrine communication is important for follicular growth and maturation. Although the signal network between oocytes and the surrounding granulosa cells is not widely known, it is currently suspected that some members of the TGF- β superfamily, for example, BMP-15 and GDF 9, have important roles. BMP-15 along with GDF 9 causes cumulus expansion by activating the expression of several genes, including hyaluronan synthase 2 (HAS 2), cyclooxygenase 2 (COX 2), and gremlin 1 (GREM 1).⁶

In this study the lowest BMP-15 expression was found in the endometriosis group, and the highest mean was found in the endometriosis + BMSCs group. However, when comparisons were made between groups, we did not find statistically significant differences. The expression of BMP-15 in the endometriosis group was the lowest among the groups. This indicates that the presence of a disorder in folliculogenesis can be seen from a decrease in BMP-15 expression. This is in accordance with the results of Sato et al. study which states that endometriosis causes PI3K pathway dysregulation.¹⁰

This result was consistent with a study of Liu et al., who found that PI3K pathway disorder in oocytes causes infertility in mice with an increase in FoXo3a which directly decreases BMP-15 expression, which can then interfere with paracrine communication from granulosa, oocyte and theca cell cells, resulting in folliculogenesis disorder.¹¹ Otsuka's study also shows that BMP15 also plays a role in the regulation of cumulus cell apoptosis. In bovine ovary, the removal of granulosa cells from cumulus oocyte complex (COC) will trigger apoptosis. This apoptosis can be prevented by providing BMP-15.¹²

Follicle is a functional unit of the ovary and each follicle consists of oocytes surrounded by one or more somatic cell layers. In order for the function of steroidogenesis and ovulation to be realized, the follicle must develop through a series of highly coordinated stages of development.¹³ Follicle development is a complex process involving signals between organ systems.¹⁴

Follicle develops through primordial, primary, and secondary stages before the antrum/cavity is formed in the follicle.¹⁵ Primordial follicles are the basic reproductive units which present as dormant oocyte pools. Morphologically, the primordial follicle consists of a primary oocyte surrounded by flat-layer epithelium granulosa cells and basement membrane.¹⁶ Along with the development of maturation, granulosa cells become cuboidal and these follicles are called primary follicles.¹⁷ Development of secondary follicles begins with the presence of a second layer of granulosa cells. This involves changes in granulosa cells and the acquisition of theca cells. Then, the follicles develop into tertiary follicles. This phase is characterized by the formation of antrum/cavity in the follicle.¹⁶

In this study Graafian follicles count in the endometriosis group was the lowest among the groups. Then, a comparative test was conducted to find the level of significance between groups. The results showed a comparison of the average number of Graafian follicles per group, where the Graafian follicles count in endometriosis group differed significantly from that in the endometriosis + BMSCs group. This showed that bone marrow mesenchymal stem cell transplantation improved somatic environment of the ovary, as characterized by improvement in folliculogenesis.

Lee et al stated that administration of bone marrow stem cells activates oogenesis directly or indirectly. Directly, stem cells activate the inhibited cell cycle, and indirectly these cells stimulate the microenvironment of the damaged cell.¹⁸ The administration of stem cells can also affect local stem cells that already exist in the ovary or stem cells outside the ovary to homing to the ovary,

thereby improving the micro-environment in the ovarian follicle area.¹⁹

Hendarto et al., in their study on the ovaries of mice that received cisplatin, found that folliculogenesis was lower compared to that of the controls. Cisplatin will destroy oocytes and granulosa cells and disrupt the secretion of growth factors. The result of this disorder is the reduction in follicular growth in the group receiving cisplatin. The administration of bone marrow transplantation has succeeded in repairing oocytes and granulosa cells and the production of growth factors, with the final result of the folliculogenesis improvement. This folliculogenesis repair is the basis for further studies regarding the mechanism of mesenchymal bone marrow stem cells in improving folliculogenesis.²⁰

A subsequent study by Santoso, who provided rat bone marrow stem cell therapy in polycystic ovary syndrome models to observe folliculogenesis, found that folliculogenesis examination using ovarian Haema-toxillin eosin staining showed folliculogenesis improvement in the treatment group, which was characterized by improved follicle formation from the primary to Graafian follicles.²¹

This study proves that bone marrow mesenchymal stem cells will be homing towards ovarian follicles damaged by endometriosis and subsequently normalize the somatic environment in the area. This will improve ovarian cellular communication. Furthermore, folliculogenesis starts normally again, which is indicated by the occurrence of growth process and the increase the number of Graafian follicles count.

CONCLUSION

Endometriosis mice model with bone marrow stem cell transplant showed no difference in BMP-15 expression in each group, but revealed significant differences in de Graaf follicles.

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