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Chamomile Infusion Reduces Ovarian Weight and Abdominal Vascular Permeability in a Rat Model of Ovarian Hyperstimulation Syndrome

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ABSTRACT

Introduction: The process by which new blood vessels are formed from pre-existing vessels is called angiogenesis. Regarding chamomile (Matricaria chamomilla, MC) contains anti-angiogenesis properties, Herein; the effect of MC infusion on ovarian hyperstimulation syndrome (OHSS) was evaluated using an experimental model of OHSS.

Methods: The sample (10 g) of the shade dried plant material was added to 1000 mL of boiling distilled water. This infusion kept for 10 min, then filtered and dried. OHSS was induced through the intra-peritoneal injection of pregnant mare serum gonadotropin (PMSG) and hCG. Treated groups were administered with 25 mg/kg of MC extract. Body and ovary weights were measured. Vascular permeability (VP) was determined through the injection of 2 mL of 5 mM Evans Blue and staining was quantified at 600 nm using a spectrophotometry.

Result: body weight gain observed in control OHSS group were attenuated by MC extract application ($P<0.05$). Also, MC decreased the ovarian weight and diameter in OHSS group. Vascular permeability was significantly decreased in MC treated rat in compared to control OHSS rats ($P<0.05$).

Conclusion: the results of the present study in a rat model indicate that MC infusion can reduce the severity of OHSS complications by reducing vascular permeability and protein leakage.

Keywords: ovarian hyperstimulation syndrome, chamomile, vascular permeability

INTRODUCTION

The treatment of anovulatory patients can restores ovulation in anovulatory patients through the pharmacological induction of two or three follicles and more frequently for aggressive controlled ovarian hyperstimulation used in assisted reproductive technique (ART). Ovarian hyperstimulation syndrome (OHSS) occurs after administration of exogenous gonadotropin to trigger the final steps of oocyte maturation. OHSS is the most serious complication of ovulation induction [1]. OHSS can be strictly defined as the shift of serum from the intravascular space to the third space, mainly to the abdominal cavity, in the context of enlarged ovaries due to follicular stimulation. The range of clinical manifestations of OHSS is the logical consequence of the increased vascular permeability (VP). Vasoactive products and follicle stimulating hormone (FSH) medications can also lead to OHSS [2]. The complications of OHSS can classify into 3 types according to its severity degree: mild OHSS include abdominal overexpansion, ovary overgrowth, nausea, vomiting, and diarrhea, Moderate OHSS includes symptoms such as accumulation of

extracellular fluid in abdomen and thorax (ascites and hydrothorax respectively) and severe OHSS includes symptoms such as thorax and abdominal discomfort and pain, severe persistent nausea, vomiting, and hypovolemic shock [3]. The pathogenesis of OHSS is poorly understood. However, the ovarian renin-angiotensin system and secretion of an angiotensin II-like substance in the presence of high concentrations of estrogen and increased capillary permeability might play a role in OHSS development [4, 5].

Matricaria chamomilla (MC) are widely used to treat some diseases. Nowadays, MC is a highly favored and much used in as various remedies in the Iranian traditional medicine. It is showed that MC contains anti-angiogenic substances which suppress angiogenesis processes. The anti-angiogenic property of MC has made this plant highly regarded for the treatment of diseases with a pathophysiological basis of angiogenesis and vascular permeability includes OHSS. On the base of these evidences, we encouraged to explore the potential role of MC infusion on OHSS consequences using experimental model of OHSS.

Materials and methods

Preparation of Plant infusion

An infusion was also prepared from the shade dried plant material. The sample (10 g) was added to 1000 mL of boiling distilled water. This infusion left to stand for 10 min and then filtered. The obtained infusion was dried for use.

Animals and experimental groups:

Immature female Wistar rats (40 - 45 g), fed freely with a standard diet and maintained under standard situation (12dark /12 light, temperature: 27 degree of centigrade). The rats were randomly allocated to 4 groups and treatments were started at day 22 of life. The control rats (group 1, n= 8) received saline 0.2 ml only for five consecutive days. OHSS rats (group 2, n= 8) received subcutaneously 10 IU of pregnant mare serum gonadotropin (PMSG) for 4 consecutive days followed by 30 IU of human chorionic gonadotropin (hCG) to induce OHSS. Treatment rats (Groups 3 and 4, n= 7) received intraperitoneally MC at doses of 10 or 25 mg/kg two hours before each PMSG or hCG administration [6]. Experimental groups are summarized as follow:

Group 1 (control):

controls rats received vehicle (saline 0.2 ml) from start at day 22 till to terminate day 26

Group 2:

(OHSS): received 10 IU PMSG for the 4 days + 30 IU hCG on day 26

Group 3 and 4:

(OHSS + MC 10 or 25): received 25 or 50 mg/kg MC before PMSG or hCG.

Measurement of body weight and ovary size

Body weights were measured by using a **Sartorius** BP610 balance with scale 1 gram. Ovaries diameter were measured by a digital caliper.

Vascular permeability assessment:

Under ketalar anesthesia (75 mg/kg), 0.2 ml of 5 mM Evans Blue dye was injected. After 30 minutes and shaking occasionally, the peritoneal cavity was irrigated with 5 ml of 0.9% sterile saline. The injected fluid was removed and centrifuged at 900 × *g* for 12 min. Evans Blue concentration was spectro-photometrically measured at 600 nm (Shimadzu spectrophotometer Model UV-1700, Japan) [7].

Results

The results are shown in table 1. Body weight increased in OHSS rats and MC at dose of 25 mg/kg notably decreased body weight compared to OHSS group ($p<0.05$). Ovarian weight and diameter increased in OHSS ($P<0.01$) and treatment of rats with MC decreased both of these variable significantly ($p<0.05$). The levels of vascular permeability (Evans blue concentration) in the OHSS groups were significantly higher than that of the control group ($P<0.01$). MC treated rats exhibited lower vascular permeability than the OHSS group ($p< 0.05$).

Table 1. Comparison of the different variable between the experimental Groups

	Group 1 (control)	Group 2 (OHSS)	Group 3 (OHSS + MC 10)	Group 4 (OHSS + MC 25)
Body weight (g)	45.7 ± 3	57.2 ± 5*	58.15 ± 4	50.1 ± 6¥
Ovarian weight (mg)	107 ± 10	281 ± 12**	258.3 ± 14	198.4 ± 11¥
Ovarian diameter (mm)	2.3 ± 0.37	4.1 ± 0.51*	3.28 ± 0.68	2.88 ± 0.42¥
Evans blue concentration(µg/100mg)	10 ± 1.4	23.6 ± 6.47**	18.44 ± 3.88	12.69 ± 3.74¥

***** Or ** showed $p<0.05$ or $P<0.01$ compared to control group, respectively.

¥ showed $p<0.05$ compared to OHSS group

Discussion

OHSS is the most serious and critical complication of ovulation induction. OHSS with a rare prevalence causes serious complication in 5–10% of patients treated for ovulation induction therapy, and the severe form takes place in 0.5–5.0% (8, 9). It is widely accepted that the main clinical components of this syndrome are marked enlargement of the ovaries, which contain luteal cysts and hemorrhagic cysts along with the shifting of fluid to the third space, including the peritoneal cavity (Golan et al., 1989).Treatment of OHSS is necessary and urgent because it almost is life threatening. As our result shown, body and ovary weight and vascular permeability decreased strikingly in the MC treated groups compared to the OHSS group. Therefore, MC is a plant material that could potentially prevent and alleviate the serious consequences of OHSS.

MC infusion are composed of several medicinal ingredients.In previous studies, the anti-tumor activity of various preparations of chamomile has been reported. In addition, flavonoids such as flavonols and flavones, phenolic acids and their derivatives were found in this plant [10, 11]. In another study, the anti-angiogenic activity of chamomile extract (and the main phenolic compounds (apigenin, apigenin-7-O-glucoside, caffeic acid, chlorogenic acid, luteolin and luteolin-7-O-glucoside) through enzymatic assay using the intracellular domain of VEGFR-2 tyrosine kinase .The presence of chemical compounds in the chamomile plant, such as luteolin, apigenin and apigenin-7-O-glucoside, which inhibits the phosphorylation of VEGF tyrosine kinase receptor, which inhibits the activity of this receptor, can be one of the mechanisms of this effect of chamomile infusion[11] .

Conclusion

We observed a significant decrease in body weight, ovary weight and size in MC treated OHSS model. Thus, the MC may have the ability to prevent OHSS consequences. Results of the study can have important implications for the development of female infertility adjuvant drugs for OHSS prevention.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

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