

HAMILTON ANXIETY SCALE (HAMA) IN INFERTILE WOMEN WITH ENDOMETRIOSIS AND ITS CORRELATION WITH MAGNESIUM LEVELS IN PERITONEAL FLUID

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SUMMARY

Background: Endometriosis is a complex disease that can result in substantial morbidity, including chronic pain, dysmenorrhea and dyspareunia. There are contradictory reports regarding the connection between acute and chronic stress and magnesium levels in body fluids.

Subjects and methods: A prospective study included 87 patients undergoing laparoscopy. The study group included 40 women with endometriosis and the control group consisted of 47 women with other causes of infertility. The levels of fright were determined using HAMA scale. The measurements of Mg levels were performed using biochemical analyzer "Monarch Plus".

Results: One day before the operation, HAMA score was 9.54 ± 7.34 in the women with endometriosis, and 6.69 ± 5.51 in the women without endometriosis. The morning before the operation, HAMA score was 8.64 ± 8.10 in the women with endometriosis, and 4.29 ± 2.29 in the women without endometriosis. The second postoperative day, HAMA score was 8.96 ± 7.60 in the women with endometriosis and 6.92 ± 5.16 in the women without endometriosis. Higher HAMA score in the women with endometriosis, in comparison with the control group, in all three time periods has been found, but the differences were not statistically significant ($p > 0.05$). A negative correlation between the concentration of Mg in peritoneal fluid and HAMA score was found in the control group ($p < 0.01$).

Conclusions. In infertile women without endometriosis a correlation between Mg concentration in peritoneal fluid and HAMA score was found. No such correlation was found in the women with endometriosis, possibly due to a systemic disorder in endometriosis that might affect Mg transport through the cell membrane.

Key words: endometriosis - HAMA scale - Mg

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INTRODUCTION

Endometriosis is a complex condition that requires a serious and responsible approach from both the doctor and the patient. It is also an estrogen-dependent disorder that can result in substantial morbidity, including pelvic pain (on average, pelvic pain symptoms begin to manifest ten years before the diagnosis is made), progressive dysmenorrhea, dyspareunia, infertility and repeat surgeries (Huang 2008, Gamulin et al. 2005). Chronic Fatigue Syndrome, that often

manifests with widespread myalgia and arthralgia, cognitive difficulties and other somatic and mental symptoms, as well as various autoimmune/inflammatory diseases, are also more often found in women suffering from endometriosis than in the general population (Sinai et al. 2002). Also, women with endometriosis are often included in many diagnostic and therapeutic procedures for long time periods, they are exhausted and tend to react more strongly to stressors.

There are contradictory reports regarding the connection between acute and chronic stress, and

magnesium (Mg) levels in body fluids (Takase et al. 2004, Teng et al. 2008). Also, catecholamines and physical exercise are known to influence the metabolism of several minerals in man, but the effects on magnesium (Mg) have been scarcely investigated (Joborn et al. 1985). Some findings indicate that stress, whether physical (i.e. exertion, heat, cold, trauma-accidental or surgical, burns), or emotional (i.e. pain, anxiety, excitement or depression), increases need for Mg (Seelig 1994). Although it has been reported that chronic stress decreases intracellular magnesium levels, the effects of chronic mental and physical stress on the autonomic activity, and on intracellular magnesium levels, have not been fully investigated in humans (Takase 2004). The precise relationship between a complex chronic disease such as endometriosis and magnesium metabolism remains unknown at present. Also, there are very few data in the literature concerning acute stress and Mg concentrations in various body fluids. Although, recently there have been some attempts to establish the connection between stress and Mg levels in animal models, no clinical trials have been done to clarify this issue. In this work we investigated the relationship between the severity of anxiety symptoms and magnesium levels in peritoneal fluid in infertile female patients with and without endometriosis, using the Hamilton Anxiety scale to determine preoperative stress (usually caused by worry about the course and outcome of the operation, as well as other factors), and postoperative stress (worry about the outcome, postoperative pain etc.).

SUBJECTS AND METHODS

A prospective study included 87 patients undergoing laparoscopy at the department of infertility of the University Clinic of Gynecology and Obstetrics “Narodni front”, Belgrade, Serbia. The study group included 40 infertile women with endometriosis undergoing laparoscopy. The control group consisted of 47 infertile women diagnosed with other causes of infertility: Polycystic ovary syndrome (PCOS), fallopian tube obstruction, uterine fibroids, adhesions and cysts. Samples of peritoneal fluid were obtained from the pouch of Douglas during laparoscopic surgery.

The severity of anxiety symptoms was measured using The Hamilton Anxiety Scale (HAS or HAMA) one day before the operation, the

morning before the operation and on the second postoperative day (Hamilton 1959). The HAMA was administered by an interviewer who asked a semi-structured series of questions related to symptoms of anxiety. The interviewer then rated the individuals on a five-point scale for each of the 14 items. Seven of the items specifically address psychic anxiety and the remaining seven items address somatic anxiety. For example, the third item specifically addresses fears related to anxiety, the fifth item addresses insomnia and sleeping difficulties related to anxiety, and the tenth item addresses respiratory symptoms related to anxiety. According to Hamilton, examples of psychic symptoms elicited by the HAMA interview include a general anxious mood, heightened fears, feelings of tension, and difficulty concentrating. Examples of somatic symptoms include muscular pain, feelings of weakness, cardiovascular problems, and restlessness. For the 14 items, the values on the scale range from zero to four: zero means that there is no anxiety, one indicates mild anxiety, two indicates moderate anxiety, three indicates severe anxiety, and four indicates very severe or grossly disabling anxiety. The total anxiety score ranges from 0 to 56. The seven psychic anxiety items elicit a psychic anxiety score that ranges from 0 to 28. The remaining seven items yield a somatic anxiety score that also ranges from 0 to 28.

Measurements of Mg levels were done blindly using Monarch Plus[®] automatic analyzer.

We also measured red blood cell (RBC) concentrations in peritoneal fluid as a potential sign of hemolysis in the samples.

Statistical analysis was done using nonparametric tests (Spearman rank correlation, Wilcoxon–Mann–Whitney test).

RESULTS

Average age in the patients with endometriosis was 31.2 ± 5.1 years, and the average age in the control group was 30.4 ± 7.7 years.

One day before the operation HAMA score was 9.54 ± 7.34 in the women with endometriosis, and 6.69 ± 5.51 in the women without endometriosis (Table 1). The morning before the operation, HAMA score was 8.64 ± 8.10 in the women with endometriosis, and 4.29 ± 2.29 in the women without endometriosis. The second postoperative day, HAMA score was 8.96 ± 7.60 in the women with endometriosis and 6.92 ± 5.16 in the women

without endometriosis. Higher HAMA score in the women with endometriosis, in comparison with the control group, in all three time periods has been found, but the differences were not statistically significant ($p>0.05$). (Table 1, Figure 1). No statistically significant difference was found between HAMA scores one day before the operation, the morning before the operation and on the second postoperative day either in the experimental or in the control group.

Although Mg concentrations in peritoneal fluid were higher in the control group, no statistical significance has been found ($Z=-1.247$, $p>0.05$) (Table 2).

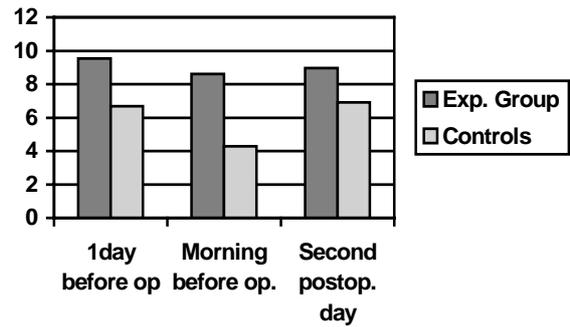


Figure 1. HAMA score in patients with endometriosis and the control group (section “Results”, 2nd paragraph)

Table 1. HAMA score in patients with endometriosis and the control group (section “Results”, 2nd paragraph)

	HAMA one day before operation	HAMA morning before operation	HAMA 2 nd postoperative day
Exp. group	9.54±7.34	8.61±8.10	8.96±7.60
Controls	6.69±5.51	4.29±2.29	6.92±5.16

Table 2. Mg concentrations in peritoneal fluid (mmol/L) (section “Results”, 3rd paragraph)

	Mg in peritoneal fluid
Exp. group	0.66±0.13
Controls	0.70±0.1692

A statistically significant positive correlation was found between HAMA score the morning before the operation and the age of the patients in the experimental group ($p<0.05$, $Z=0.532$).

A statistically significant negative correlation was found between HAMA score the morning before the operation and Mg concentrations in peritoneal fluid in the control group ($p<0.01$, $Z=-1.000$). However, no such correlation was found in the group with endometriosis.

There was no statistically significant correlation between Mg concentrations in peritoneal fluid and red blood cell (RBC) concentrations ($Z=0.493$, $p>0.05$) either in the experimental or the control group.

DISCUSSION

Mg is after potassium the most abundant cation in cells and the most abundant free divalent cation that is deeply and intrinsically involved in cellular metabolic processes. Mg-dependent enzymes appear in most metabolic pathways: for example, in many cases, there is a specific binding of Mg to biological membranes. Mg is also used as

a signaling molecule, and much of nucleic acid biochemistry requires Mg, including most of the reactions which require release of energy from ATP (Cowan 1995, Romani & Maguire 2002, Shaul 2002). In this work we found that in some women undergoing laparoscopic procedures (the patients without endometriosis), there is a strong negative correlation between the severity of anxiety symptoms (measured by Hamilton anxiety scale) and Mg concentrations in peritoneal fluid ($p<0.01$, $Z=-1.000$). This is in accordance with the findings that exogenous infusion of adrenaline significantly reduced the plasma Mg levels in healthy men and that the effect was abolished by simultaneous infusion of propranolol (Joborn et al. 1985). Also, it is known that major stresses activate not only the CRH-ACTH-cortisol axis but the adrenergic nervous system as well, that catecholamines increase rennin release by stimulation of beta-receptors, that the increase in rennin increases aldosterone secretion and that aldosterone increases magnesium excretion (Berne et al. 2004). Thus, the decreased Mg levels we found in peritoneal fluid may have been because of the higher production of endogenous catecholamines (predominantly adrenaline) in these patients. This remains to be investigated in some future research, especially given that the HAMA score in our study overall indicates relatively low level of anxiety in all subjects, in both groups. On the other hand, in endometriosis

patients, we unexpectedly did not find the correlation between HAMA and Mg levels in peritoneal fluid. The cause of this remains unclear. However, we should mention that endometriosis is a complex disorder whose pathophysiology remains unclear. It manifests with significant hormonal and metabolic changes, as well as changes in the immune system. The lack of correlation between HAMA and Mg levels in peritoneal fluid in the endometriosis patients in our study may be the result of these changes, including a possible systemic disorder in endometriosis that might affect Mg transport through the cell membrane. Therefore, we can speculate that as a result of some unknown mechanism, endometriosis changes magnesium metabolism and its relation with preoperative stress levels. However, additional research needs to be conducted in order to confirm this presumption.

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