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Original Article

Diosmin versus cabergoline for prevention of ovarian hyperstimulation syndrome

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ABSTRACT

Background: OHSS (Ovarian Hyperstimulation Syndrome) is the most serious iatrogenic complication of ovulation induction. The pathophysiology of OHSS is characterised by increased capillary permeability, leading to leakage of fluid from the vascular compartment, with third space fluid accumulation and intravascular dehydration.
Objective: This study aimed to evaluate the effectiveness of diosmin in comparison to the dopamine agonist cabergoline in preventing OHSS in high risk patients undergoing assisted reproductive technique cycles.
Methods: In this study, 200 women who were at high risk for developing OHSS were randomly allocated into two groups. Group A (Diosmin group, 100 women) and group B (Cabergoline group, 100 women). All patients were assessed every two weeks after retrieval and for 8 weeks to determine early clinical or ultrasound evidence of OHSS.
Results: There was a statistically significant reduction (P = 0.005) in the incidence of OHSS in the diosmin group (12%) compared to cabergoline group (28%). The number of severe OHSS cases in the cabergoline group (n = 13) was significantly higher (P = 0.003) than the diosmin group (n = 2). There was no difference in clinical pregnancy rate.
Conclusion: Our results concluded that diosmin was more effective in preventing severe OHSS and decreasing OHSS occurrence rates than cabergoline when used in high-risk patients.
Trial registration: Clinical trial.gov (NCT02134249).

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the most dangerous iatrogenic complication of ovulation induction in controlled ovarian stimulation cycles [1]. The incidence of OHSS ranges from 33% in mild cases to 3–6% in moderate cases while reaching only 0.1–2% in severe cases [2,3]. The pathophysiology of early OHSS remains unknown but it is clear that its appearance is mediated by the administration of hCG in COH cycles [4]. Human chorionic gonadotrophin (hCG) or luteinising hormone (LH) following controlled ovarian stimulation by follicle-stimulating hormone (FSH) is responsible for most cases of OHSS. It is the hCG action on the stimulated ovaries that leads to the production of numerous proinflammatory mediators with vascular endothelial growth factor (VEGF) as the chief player [5].

Numerous other factors have been implicated in the disease process such as angiotensin II,interleukin-6, insulin-like growth factor 1 (IGF-1) [6], epidermal growth factor (EGF), transforming growth factors (TGF) a and b, basic fibroblast growth factor (BFGF), platelet-derived growth factor (PDGF), interleukin-1b (IL-1b), and interleukin-6 (IL-6) in which they can act directly or indirectly via VEGF [7–9].

Vascular endothelial growth factor-A (VEGF-A) acts on VEGF receptor-2 (VEGFR-2) causing angiogenesis and vascular hyperpermeability. Thus, its increase in OHSS is responsible for the increased vascular permeability [10,11].

The importance of VEGF in increased vascular permeability has been demonstrated in stimulated female rats. This study confirmed that VEGF and VEGFR-2 are overexpressed in hyperstimulated rats, and are associated with an increase in vascular permeability, which may be responsible for the accumulation of ascitic fluid in the syndrome [12].

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The main pathophysiological feature of OHSS is increased capillary permeability, which leads to fluid shift to the third space [1]. This results in ascites or, less commonly, pleural and pericardial effusions. Women in acute severe cases are usually presented by hypovolaemia, with a typical loss of 20% of their calculated blood volume [13].

In a group of women with polycystic ovarian syndrome and hyperprolactinemia, cabergoline administration was reported to reduce the incidence of OHSS [14]. Results obtained with animal models, and the safe clinical profile of dopamine agonists, have led to studies on humans. Concerning the safety of cabergoline use during infertility treatment: fertilization, implantation and pregnancy rates were similar to matched controls [15].

Four systematic reviews and meta-analyses have revealed that cabergoline reduces the incidence of moderate/severe OHSS without affecting implantation, pregnancy and miscarriage rates [16–19].

The flavonoid glycosides diosmin and hesperidin are present naturally in citrus fruit. Micronized purified flavonoid fraction (MPFF) is a semisynthetic drug which is composed of 90% micronized diosmin and 10% hesperidin [20].

MPFF is used in a broad spectrum of patients to treat varicose veins and venous ulcers, hemorrhoids and lymphatic insufficiency [21,22]. In these conditions, MPFF exerts a venotonic action, decreasing venous reflux, and thereby relieving the edema through providing effective venous drainage [23].

Diosmin is a hesperidin-derivative bioflavonoid. Flavonoids have been demonstrated to exert anti-lipoperoksidant, anti-tumoral, anti-platelet, anti-ischemic, anti-allergic, and anti-inflammatory activities [24].

MPFF has been shown to interfere between the leukocytes and the endothelium [25]. MPFF normalizes the synthesis of free radicals and prostaglandins to alleviate the microcirculatory dysfunction [26]. MPFF has been shown to decrease leukocyte adhesion to the vascular endothelium and the levels of granulocyte and macrophage infiltration into the inflamed tissues. The decrease in release of oxygen free radicals, cytokines, and proteolytic matrix metalloproteinases from activated inflammatory and endothelial cells, results in lowering of inflammation, decreased microvascular permeability and decreased leukocyte-dependent endothelial damage [25,27].

Diosmin causes a reduction in the release of inflammatory mediators, such as prostaglandin E2 (PGE2) and thromboxane A2 (TxA2) [28]. Furthermore, diosmin causes significant decreases in plasma levels of endothelial adhesion molecules and reduces neutrophil activation, thus providing protection against microcirculatory damage [29,30].

These effects of MPFF can be accredited to the antiinflammatory, microcirculatory, and antioxidant effects by decreasing the level of hydroxyl free radicals [31], increasing free SH-group concentration, and natural scavenger capacity [32]. MPFF decreases vascular permeability more than any of its single constituents, suggesting that the flavonoids present in its formulation have a synergistic action [33].

In a study where 20 patients with chronic venous disease were treated with MFFP (Diosmin 500 twice daily for 60 days). VEGF plasma levels were significantly decreased in the patients after treatment (98–57 pg/ml) [34].

Aim of the study: Is to determine the efficacy of diosmin in comparison to cabergoline in preventing OHSS in high-risk women undergoing ICSI cycles.

2. Patients & methods

This was an interventional comparative clinical trial conducted at the department of obstetrics and gynecology, Benha University Hospital and a private fertility center from April 2014 till December 2015, after approval of the study protocol by the local ethical committee.

Patients enrolled in the study were infertile women undergoing ICSI with one of the following criteria: previous episodes of OHSS, polycystic ovaries (i.e., >24 antral follicles present on baseline ultrasound examination), high AMH (>3.0 ng/mL), large number of small follicles (8–12 mm) seen on ultrasound during ovarian stimulation, high s.E2 at hCG trigger (E2 > 3000 pg/ml or rapidly rising s.E2), presence of >20 follicles by ultrasound on day of retrieval or large number of oocytes retrieved (>20).

All participating patients provided written informed consent at their first visit. Each participant underwent a complete evaluation including: clinical history, physical examination, ultrasound evaluation & hormonal profile.

Two hundred high-risk patients after meeting these inclusion criteria, were randomly divided into: **Gp A:** were given 2 tab. (500 mg)/8 hs diosmin orally, for 2 weeks starting at the day of HCG injection. **Gp B:** received 1 tab. (0.5 mg)/day cabergoline orally for 8 days starting at day of HCG injection.

The occurrence and severity of OHSS was defined according to the classification described by Golan et al. [3] Complaints of abdominal discomfort, nausea, vomiting and ultrasound evidence of enlarged ovaries (5–12 cm) and/ or the detection of ascites defined the occurrence of moderate OHSS.

The presence of clinically evident ascites and/or hydrothorax, increased blood viscosity and coagulation abnormality or lab. Investigation of increased hematocrite level (>45%) or decreased *S. albumin* (<35 g/l) defined the occurrence of severe OHSS. Patients with severe OHSS were hospitalized. Onset of OHSS within 10 days of ovulatory trigger was defined as early onset OHSS while beyond 10 days was defined as late onset OHSS.

Clinical and ultrasound examinations were performed on the day of embryo transfer, then weekly to detect the occurrence of OHSS. All patients were instructed to contact us if they experienced difficulty in breathing, recurrent vomiting, decreased urine volume, dizziness on standing, abdominal pain, enlargement of the abdomen and rapid weight gain and were examined as needed.

Women were monitored on an outpatient basis via phone contact and visits until menstruation occurred or until fetal heart activity was detected in pregnant patients.

The primary outcome was an evaluation for the development of OHSS in the participants. Implantation rate and clinical pregnancy rate were secondary outcomes.

3. Results

There were no statistically significant differences between the diosmin and cabergoline groups concerning age, no. of total ampoules of FSH used, duration of infertility, antral follicle count (AFC), body mass index (BMI), length of stimulation days, E2 level on the day of hCG trigger and the total number of the retrieved oocytes (Table 1).

OHSS occurred in 12 cases in the diosmin group versus 28 cases in the cabergoline group showing a statistically significant reduction (P = 0.005) in the diosmin group. Also severe OHSS was 2% in the diosmin group compared to 13% in the cabergoline group. The difference was statistically highly significant (P = 0.003) (Table 2).

The secondary outcomes concerning fertilization, implantation, clinical pregnancy and multiple pregnancy rates between diosmin and cabergoline groups showed no statistically significant differences (Table 3).

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