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Calcium Dobesilate versus Cabergoline for Prevention of Ovarian Hyper Stimulation Syndrome

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Abstract

Background: OHSS (Ovarian Hyper stimulation Syndrome) is the most serious iatrogenic complication of ovulation induction. The pathophysiology of OHSS is characterized 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 Calcium dobesilate (CaD) 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 (Calcium dobesilate group, 100 women) and group B (Cabergoline group, 100 women). All patients were assessed weekly 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 Calcium dobesilate (CaD) 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 CaD group (n=2). There was no difference in clinical pregnancy rate.

Conclusion: Our results concluded that Calcium dobesilate (CaD) was more effective in preventing severe OHSS and decreasing OHSS occurrence rates than cabergoline when used in highrisk patients.

Keywords: Cabergoline; Calcium dobesilate; Infertility; ICSI; Ovarian hyperstimulation syndrome

Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of most serious complications in assisted reproductive technology (ART). It is a potentially life-threatening condition characterized by ovarian enlargement, pleural effusion, ascites, oliguria, hemoconcentration and thromboembolism [1,2]. The incidence of mild OHSS is 20%–33% within all in vitro fertilization (IVF) cycles, an incidence of 3%–6% for moderate OHSS and severe OHSS occurring in 0.1%–2% of cycles [3]. The mortality rate of OHSS is low, with an estimated incidence at 1:400 000–1:500000, and the incidence of hospitalization is 1.8% [3,4].

The pathophysiology of OHSS is not fully understood; however, increased capillary permeability due to production of ovarian vasoactive substances such as angiotensin and vascular endothelial growth factor (VEGF) with a resultant third space fluid loss appears to be the main feature. Many substances involved in vascular permeability regulation have been investigated as potential causes of OHSS; however, vascular endothelial growth factor (VEGF) has emerged as the main substance implicated in its pathogenesis. VEGF exhibits both vasoactive properties and increased ovarian expression during the pathogenesis of OHSS, suggesting that it plays a major role in the development of this potentially life-threatening condition [5,6].

Another pathophysiological mechanism implicated in OHSS is the intraovarian renin angiotensin system (RAS). The ovarian RAS is involved in regulating vascular permeability, angiogenesis, endothelial proliferation, and prostaglandin release. hCG causes a strong activation of the RAS, evidenced by high renin activity in the follicular fluid of women with OHSS [7]. Overstimulation of this cascade, together with increasing VEGF levels, is postulated to synergistically potentiate OHSS [8].

Risk factors for development of OHSS include low body mass index, younger age, higher ovarian reserve, and higher doses of gonadotropins and history of previous OHSS [9]. A frequent endocrine disorder of women, the polycystic ovarian syndrome, is a known risk factor for the development of OHSS [10].

The literature describes two main clinical forms of OHSS; an early form relating to the ovarian response to stimulation, which happens to be a sharp effect of exogenous hCG administration. It takes place during the first 9 days after oocyte retrieval [11]. The late form correlates poorly with the ovarian response: it correlates better with endogenous hCG produced by implanting an embryo or with hCG administration for luteal phase support. It occurs after the initial 10-day period and its management is clinically more difficult [12].

Calcium dobesilate (CaD) (calcium dihydroxy2,5benzenesulfonate) is a vascular protective compound which was revealed to be the most effective member of a new family of efficient fibroblast growth factor

[FGF] inhibitors [2]. It is used for the management of chronic venous insufficiency symptoms, diabetic retinopathy and haemrrhoids. Calcium dobesilate has an inhibitory effect on capillary permeability by the regulation of serotonin, bradykinin and histamine, improve erythrocyte aggregation and blood viscosity [13]. Angulo et al. reported that Calcium dobesilate (CaD) inhibits the main vascular responses in vitro and *in vivo* stimulated by VEGF [14].

Dopamine agonist drugs as cabergoline has been found to reverse VEGFR-2-induced vascular permeability and has been found to reduce the incidence of moderate OHSS when compared with placebo in *in-vitro* fertilization (IVF) patients at risk of OHSS without affecting implantation and pregnancy rates in IVF patients [15].

Patients and methods

We conducted this prospective randomized study at Department of Obstetrics and Gynecology, Benha University Hospital, since April 2013 till December 2015, after approval of the study protocol by the Local Ethical Committee. All participating patients provided written informed consent at their first ultrasound visit. Each participant underwent a complete evaluation including clinical history, physical and examination and hormonal profile. The patients were down regulated to the long protocol with gonadotropins such as HMG, purified urinary follicular stimulating hormone (merional).

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 to 12 mm) seen on ultrasound during ovarian stimulation, high E2 at hCG trigger (E2>3000 pg/ml or rapidly rising E2), presence of >20 follicles by ultrasound on day of retrieval or large number of oocytes retrieved (>20).

It was a comparative study where in the 200 high-risk patients after meeting the strict inclusion and the exclusion criteria, were randomly divided into two groups with 100 subjects in each group. The women with even registration numbers were in Group I and were administered 1 cap/8 h (CaD) (500 mg) orally at day of HCG injection and for 21 days while that who had odd registration numbers belonged to Group II and received 1 tab/day Cabergoline(0.5 mg) orally at day of HCG injection and for eight days.

Diagnosis of OHSS made according to the criteria of Golan et al. [16]:

Mild OHSS was classified as: Grade 1 (abdominal distension and discomfort) and Grade 2 (features of grade 1 plus nausea, vomiting and/or diarrhea; ovaries are enlarged from 5 to 12 cm),

Moderate OHSS As grade 3 (features of mild OHSS plus ultrasonic evidence of ascites).

Severe OHSS as Grade 4 (features of moderate OHSS plus evidence of ascites and/or hydrothorax and breathing difficulties) and Grade 5 (all of the above, plus change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormality, and diminished renal perfusion and function).

All women were weighed and haematological tests were performed immediately following oocyte retrieval and again weekly for 8 weeks. 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.

Evaluation of the subjects for the development of OHSS was the primary outcome measure and pregnancy rate was the secondary outcome measure.

Results

A total of 200 women were evaluated for risk factors of OHSS, who fulfilled the required inclusion criteria, were included in the study. One hundred patients in each group completed the study.

Table 1 lists the patient characteristics and infertility status of the two groups. No significant differences were found in mean age (p=0.18), body mass index (BMI) (p=0.28), duration of infertility (p=0.53) and estradiol on the day of hCG injection (p=0.83) in both groups. The mean No. of total mFSH (merional) ampoles, duration of gonadotropin administration of E2 on the day of hCG, total number of antral follicles and retrieved oocytes were similar in both groups (p=0.11, p=0.55, p=0.75, p=0.63, p=0.88 respectively).

variable	(CaD) group	Cabergoline group	P value
Female age (years)	28.52 ± 4.67	29.54 ± 5.36	0.18
No. of total mFSH(merional) (75 IU/ Amp)	25.45 ± 3.62	26.06 ± 3.67	0.11
Duration of infertility (years)	6.04 ± 3.38	5.76 ± 2.87	0.53
AFC	23.85 ± 3.23	23.51 ± 3.46	0.75
BMI (kg/m²)	25.48 ± 3.84	25.8 ± 3.73	0.28
Length of stimulation (days)	9.66 ± 1.85	9.42 ± 1.57	0.83
E2 on day of hCG (pg/ml)	4580 ± 717	4624 ± 580	0.63
Retrieved oocytes	18.79 ± 4.02	18.44 ± 3.67	0.88

Table 1: Demographic characteristics of women in the (CaD) and cabergoline groups.

Follow-up of the patients showed that OHSS was significantly lower in the (CaD) group (12/100) than cases in cabergolin group (28/100) (p=0.005) and that severe OHSS cases were significantly more common in the cabergolin group (13/100) than in (CaD) group (2/100) (P<0.003) (Table 2).

variable	(CaD) group	Cabergoline group	Z test	P value
OHSS (%)	12	28	-2.829	0.005
Severe OHSS (%)	2	13	-2.953	0.003

Table 2: OHSS incidence in diosmin group vs. cabergolin group.

All OHSS cases in both groups were early onset OHSS. The patients with mild and moderate OHSS from both the study groups were monitored on an outpatient basis until the resolution of signs and symptoms. All the severe cases in our study were grade 4 of Golan et al. criteria and treated as outpatient. Only two cases in the cabergolin group was hospitalized with oliguria (urine output<500 cc per 24 h) and Haemoconcentration (hematocrit >45%).

Fertilization rates, the implantation, chemical and clinical pregnancy and multiple pregnancy rates as well as the number of miscarriages were similar in both groups (Table 3).

variable	(CaD) group	Cabergoline group	Z test	P value
Fertilization rate (%)	72	69	0.465	0.64
Implantation rate (%)	68	66	0.3	0.76
Clinical pregnancy rate(%)	59	56	0.429	0.67
Multiple pregnancy rate (%)	22	19	0.525	0.6
First trimester miscarriages n (%)	5	4	0.341	0.73

Table 3: IVF/ICSI outcomes between two groups.

The side effects attributed to the two drugs are compared in Table 4. Cabergoline was responsible for significantly more Dizziness (P=0.02) than (CaD), but there was no statistically significant difference between the two groups regarding the other side effects.

variable	(CaD) group	Cabergoline group	Z test	P value
Nausea (%)	8	11	-0.724	0.47
Vomiting (%)	7	10	-0.76	0.45
Headache (%)	7	4	0.93	0.35
Epigastric pain (%)	6	11	-1.268	0.2
Dizziness (%)	5	15	-2.357	0.02

Table 4: A comparison of the adverse events between the two groups.

Discussion

There are different preventive measures for OHSS which include identifying at risk women, reducing the gonadotropin dose and duration, adjuvant metformin use and aromatase inhibitors use. It also includes coasting, cycle cancelation, GnRH use for trigger in antagonist cycles, decreasing the hCG dose, no hCG for luteal phase support, colloid, albumin, hydroxyethyl starch, freezing of all embryos, and/or cabegoline [17].

This study included 200 high risk cases for OHSS. Calcium dobesilate (CaD) treatment reduced OHSS to 12% compared to 28% in the cabergoline group. The difference was statistically highly significant (P=0.005). Moreover, Calcium dobesilate (CaD) decreased severe OHSS to 2% compared to 13% in the cabergoline group (P=0.003). The clinical pregnancy rate (PR) and miscarriage rate were not statistically significant in both groups.

Cabergoline is a dopamine antagonist that prevents the excessive increase in VEGF mediated vascular permeability encountered with OHSS through its antiangiogenic properties [18]. Different studies have evaluated its use as a preventive strategy for OHSS with a varying dose from 0.25 mg up to 1.0 mg. Recently, a systematic review and metaanalysis of eight randomized controlled studies (n=858 women) comparing cabergoline versus placebo, albumin or no treatment for the prevention of severe OHSS were published. There was evidence of a statistically significant reduction in the incidence of severe OHSS in the cabergoline group (RR: 0.38, 95% CI: 0.29–0.51) [19].

Many studies used different regimens such as, 0.5 mg tablet of cabergoline for 12 days beginning on the day after oocyte retrieval [20], 0.5 mg tablet of cabergoline for 8 days beginning on the day after hCG injection [21], 0.5 mg tablet of cabergoline for 3 weeks beginning on the day after oocyte retrieval [22], 0.5 mg tablet of cabergoline for 2 days, repeating 1week later, beginning on the day after hCG injection [23], 0.5 mg tablet of cabergoline for 7 days beginning on the day after hCG injection [24] and 0.5 mg tablet of cabergoline for 7 days beginning on the day after oocyte retrieval [25].

Youssef et al. conducted a meta-analysis to answer the question about the success of dopamine agonist in the treatment of OHSS. Four randomized trials entailing 570 women were included. There was evidence of a statistically significant reduction in the incidence of OHSS in the cabergoline group (OR 0.41, 95% CI 0.25–0.66) with an absolute risk reduction of 12% (95% CI 6.1–18.2%), but there was no statistically significant evidence of a reduction in severe OHSS (OR 0.50, 95% CI 0.20–1.26) [26].

Alvarez et al. [27] concluded that there is no statistical evidence of the timing of cabergoline administration (day of hCG injection versus after oocyte retrieval) on final oocyte maturation, fertilization rate or clinical outcome for the prevention of OHSS in highrisk patients. Both treatment modalities effectively decrease the incidence of severe OHSS.

Tang et al. [28] in their Cochrane Review of 230 women in 2 RCTs found cabergoline to be effective in significantly reducing the incidence of moderate OHSS (OR 0.38; 95% CI 0.19–0.78) with no significant effect on clinical pregnancy rate and miscarriage rates. A recent systemic review by Leitao et al. [29] on the issue, which considered 7 RCTs, has further established its efficacy in preventing the occurrence of moderate and severe OHSS (RR 0.38; 95% CI 0.29–0.51) as well as without a negative impact on clinical pregnancy or oocytes retrieved. Therefore, the use of cabergoline is recommended and it is suggested that treatment be commenced on the day of hCG trigger at a dose of 0.5 mg for 8 days [30].

Interestingly, one study has shown that women with PCOS are less responsive to cabergoline compared with those without PCOS, most probably due to a decreased production of dopamine and dopamine receptor expression [31]. Interestingly, dopamine agonists cannot prevent late OHSS [6].

There was no evidence of a difference in OHSS rates between cabergoline and other lines (e.g. hydroxyethyl starch, prednisolone or 'coasting' (withholding anymore ovarian stimulation for a few days). However, coasting had a lower pregnancy rate than cabergoline [32].

A current randomized controlled study with 118 women in each arm compares a complex rescue protocol to reduce the perceived high risk of OHSS with Cabergoline as the only preventive strategy [33]. Oral Cabergoline was combined with a change of protocol from agonist to antagonist protocol and reduction of gonadotropin dose, as

well as reduction of hCG dose to 5.000 IE. A risk reduction for OHSS from 13.6% in the Cabergoline-only group to 5.1% in the antagonist rescue protocol was shown (p=0.025).

Calcium dobesilate (CaD) is a synthetic product, marketed worldwide, that is classified as a vasculo-protector and veno-tonic drug. Safety studies of CaD commonly investigate various effects on hematological parameters and capillary impacts and have been described in several reports. CaD exhibits its inhibitor effect on capillary permeability through the regulation of serotonin, bradykinin, and histamine. Additionally, it reduces endothelial desquamation via nitric oxide release and synthesis. The dose-dependent microcirculatory effects of CaD were found to reduce platelet aggregation via prostaglandin inhibition and also to reduce erythrocyte aggregation and their suspension viscosity. In addition to these studies, the antiangiogenic potential of CaD was investigated in a few studies; for instance, Lameynardie et al. claimed that CaD inhibits VEGF over-expression in rat retinas [34].

After oral administration of calcium dobesilate 500 mg, maximum plasma drug concentration (Cmax) was 8 pg/ml on average 6 hours later. Protein binding was 20-25%. Plasma half-life was 5 hours and the elimination half-life varied between 2.5 and 15 hours. Eight per cent of the product administered orally was absorbed within the first 8 hours. Urinary elimination reached 50% of the dose administered 24 hours after absorption; 10% was eliminated in the form of metabolites in 24-hour urine output. Calcium dobesilate did not pass into the cerebrospinal fluid and did not cross the placenta. It appeared in very low concentration in maternal milk. No pharmacokinetic interactions have been reported in the literature [35].

Calcium dobesilate at dosages varying between 500-1500 mg/day have shown therapeutic efficacy in venous pathologies such as chronic venous disease and haemorrhoids, as well as in diabetic retinopathy. Taking into account its very wide use, the risk of adverse outcomes with this medication must be considered as minimal, of minor gravity and mainly consisting of general syndromes (fever, arthralgias, cutaneous-mucosal signs, allergies) [36].

To the best of our knowledge, this is the first study to use Calcium dobesilate (CaD) as a form of preventive measure against OHSS. The efficacy of Calcium dobesilate (CaD) in dealing with the pathogenesis, pathophysiology and complications of OHSS seems feasible. Its previous safety profile in pregnancy and this study gives a solid base reasoning for its efficiency in reducing the rate of moderate and severe cases of OHSS with a good safety profile concerning the implantation, pregnancy and miscarriage rates.

Conclusion

Calcium dobesilate (CaD) is more effective in preventing both moderate and severe
OHSS occurrence rates than cabergoline when used for highrisk patients. Calcium dobesilate (CaD) is an oral cheap drug and well tolerated by the patient. Calcium dobesilate (CaD) is safe during pregnancy. Calcium dobesilate (CaD) is a well-known drug with a new indication.

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