Comparison of cabergoline and intravenous albumin in the prevention of ovarian hyperstimulation syndrome: a randomized clinical trial

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Received: 4 October 2011 / Accepted: 28 December 2011 / Published online: 10 January 2012
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Abstract

Purpose To compare the efficacy of cabergoline (Cb2) and intravenous human albumin (HA) in the prevention of ovarian hyperstimulation syndrome.

Methods In this randomized controlled trial study, 138 women who were at high risk for developing OHSS were randomly allocated into two groups. In Group one, 20 gr of HA 20% was infused over 1 h. Group two received 0.5 mg per day of Cb2 orally for 7 days, starting on oocyte pickup day. All patients were visited seven and 14 days after oocyte

retrieval to determine early clinical or ultrasound evidence of OHSS.

Results Moderate OHSS was observed in 33 versus 14 cases in the HA and Cb2 groups, respectively, which was significantly different. The number of severe OHSS cases in the HA group was significantly higher than in the Cb2 group ($P < 0.001$).

Conclusions Prophylactic oral low dose cabergoline was more effective and less costly than intravenous human albumin in the prevention of OHSS in high-risk patients. (NCT01009567)

Capsule In the following report, we found that the oral cabergoline tablet (dostinex) is more effective and less costly than intravenous human albumin in the prevention of Ovarian Hyperstimulation Syndrome.

Electronic supplementary material The online version of this article (doi:10.1007/s10815-011-9708-4) contains supplementary material, which is available to authorized users.

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Keywords Albumin · Cabergoline · IVF outcome · Ovarian hyperstimulation syndrome

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a dangerous iatrogenic complication of assisted reproductive techniques (ART) which may cause severe morbidity and even mortality [1].

From the first suggestion of intravenous (i.v.) human albumin (HA) use for the prevention of OHSS by Asch et al. until now, there have been conflicting findings. Some studies suggested a role for albumin in the prevention of OHSS [2–4]. However, in several recent studies the effect of HA was similar to a placebo [5, 6] and less than other preventive drugs [7–9]. A recent review article reported low evidence of benefit from i.v. albumin administration at the time of ovum pickup in the prevention or reduction of the incidence of severe OHSS in high-risk women undergoing ART cycles [10]. Despite the possible side effects (febrile reaction, allergic reaction, anaphylactic shock and risk of virus transmission) [5, 8] and unsatisfactory results of i.v. albumin,

it is still commonly used for the prevention of OHSS in many ART units, including ours.

The exact etiology of OHSS is not clear, but evidence exist that vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF α), interleukin 2 and interleukin 6 contribute to the development of this syndrome [11] and administration of a dopamine agonist inhibits phosphorylation of the endothelial growth factor receptor-2 (VEGFR-2) [12]. Two studies have been performed to evaluate the efficacy of cabergoline (Cb2) as a dopamine antagonist in the rat model [12, 13]. Additionally, several studies in humans reported that Cb2 might provide a new, specific and non-toxic approach to the treatment of OHSS without altering angiogenesis [14–17]. According to previous studies optimal dosing, timing and duration of Cb2 administration are still unknown and further large randomized studies are needed to prove its usefulness in clinical practice. Therefore, we performed this randomized clinical trial to assess and compare HA with low-dose Cb2 in the prevention of OHSS in high-risk patients immediately after ovum pickup day.

Materials and methods

We designed a randomized clinical trial study to compare the efficiency of Cb2 and i.v. HA in the prevention of OHSS. The Institutional Review Board and Ethical Committee of Royan Institute approved this study. Patients signed informed consent forms before enrolling in the study.

Patients who entered the in-vitro fertilization (IVF) or IVF with intracytoplasmic sperm injection (ICSI) cycles at Royan Institute from June 2009 to December 2010 were evaluated for risk factors of severe OHSS. We defined risk factors for the development of OHSS as the existence of 20–30 follicles larger than 12 mm in diameter on the day of hCG administration, and retrieval of more than 20 oocytes. Coasting cases, women over the age of 37 years, those with a history of uterine surgery, submucosal and intramural fibromas larger than 5 cm, were excluded.

The stimulation protocol for all patients was performed according to the standard long protocol. Subcutaneous injections of Buserelin 500 μ gr (Superfact; Aventis Pharma Deutschlan, Frankfurt, Germany) were started on the 21st day of their menstrual cycles. Down regulation was confirmed by the presence of a linear endometrium as seen on ultrasonography and suppressed ovaries by serum estradiol concentrations less than 50 pg/ml. Gonadotropin stimulation commenced 14 days after suppression and continued until at least two follicles $\geq$ 18 mm were detected. Recombinant human FSH (Gonal-F; Serono Laboratories Ltd., Geneva, Switzerland) was used for follicular stimulation in all cycles. Human chorionic gonadotropin (hCG; Choriomon; IBSA), 10000 IU, was injected intramuscularly and followed 34–

36 h later by oocyte retrieval. Immediately after oocyte pickup, eligible patients were admitted to the recovery room. Patients were allocated into two groups by the Computer-based randomization method. To enroll the patient into the study, a midwife opened the sealed envelopes. Embryo culture and transfer procedures were carried out in the two groups using the same method. Luteal phase support was provided by vaginal progesterone (Aburaihan Co., Tehran, Iran), 400 mg twice a day, until the day of β -hCG assay.

After a pilot study on 30 patients in each group, with a two-sided 5% significance level, an efficacy of 80% and an anticipated dropout rate of 10%, a sample size of 70 patients per group was calculated.

Intravenous albumin group

Group one consisted of 70 infertile women considered at high risk for severe OHSS, who were randomly assigned to receive 20 gr HA (Human Albumin 20%, biotest Inc, Germany). The solution was i.v. infused over 1 h on the ovum pickup day.

Cabergoline (dostinex) group

Group two consisted of 70 infertile women with $\geq$ 20 retrieved oocytes who were randomly selected for oral Cb2 treatment. Patients received 0.5 mg of Cb2 (Dostinex[®]; Pharmacy Italia) for 7 days at bedtime starting on the day of oocyte pickup.

All women were weighed and haematological tests were performed immediately following oocyte retrieval and again 7 and 14 days later. Trans-abdominal or trans-vaginal ultrasound was done to detect mean ovarian diameters as well as degree of fluid in Douglas pouch. Patients were educated about measuring daily weight and urine volumes and instructed to report by phone any increased edema of the extremities and abdomen, difficulty breathing, dizziness with position changes or when standing, decreased urinary output and severe abdominal pain. Patients were told to immediately refer to the institute if any of the above symptoms were present. Diagnosis of OHSS was made according to the criteria of Golan et al. [18]. 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).

Table 1 Demographic characteristics and infertility status of women in two groups

Variables	HA (n=69)	Cb2 (n=69)	P-value
Age (y) ^q	28.08±4.6	29.03±4.2	0.61
BMI (Kg/m ²)(Mean±SD) ^q	24.9±3.8	24.8±3.3	0.12
Positive history of PCOS ^q	56.5%	47.5%	0.31
FSH level at 2nd day of cycle (Mean±SD) ^q	5.2±1.9	5.9±2.8	0.1
LH level at 2nd day of cycle (Mean±SD) ^q	6.7±5.5	5.3±4.3	0.45
E2 on day of hCG (pg/mL) ^q	3027±1226	2887±1180	0.47
Duration of infertility	76±3.4	7.3±3.6	0.7
Type of infertility [N(%)] ^q			0.17
Primary	62 (89.9)	66 (95.7)	
Secondary	7 (10.1)	3 (4.3)	
Cause of infertility [N(%)] ^q			
Ovulatory factor (PCOS)	14 (20.2)	11 (17.2)	NS
Uterine factor	9 (13.2)	5 (7.2)	NS
Male factor	21 (30.4)	34 (49.2)	0.03*
Multiple factor	20 (29)	15 (21.7)	NS
Unexplained	5 (7.2)	4 (5.7)	NS

q Chi-square test

^q Student's *t*-test

*significant difference between groups in male factor cases

HA human albumin

Cb2 Cabergoline or Dostinex

NS no significant difference

According to Carizza et al., we defined OHSS with an onset ≥ 10 days after oocyte retrieval as “late” and OHSS with earlier onset as “early” OHSS [15]. All the mild and moderate cases were managed as symptomatic. All the monitoring was done by a co-investigator gynecologist and haematological tests were done in the Royan Institute laboratory using the same method and normal values.

Statistical analysis

Statistical analysis was performed using an SPSS (Version 16, SPSS Inc., Chicago, IL, USA) and Stata/SE 11.0 package.

Chi-square test, student *t*-test and ordinal logistic regression were performed to evaluate the statistical differences between the variables. $P < 0.05$ was considered significant.

Results

Sixty-nine 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, body mass index (BMI), duration of infertility, type of infertility, basal FSH, LH levels and estradiol on the day of hCG injection in both groups. There was a significant difference in

Table 2 Ovarian stimulation outcomes and Clinical and laboratory follow up of the patients

Variables	HA (n=69)	Cb2 (n=69)	P-value
No. of total recombinant hFSH (75 IU/Amp) ^q	22.2±11.5	25.4±11.8	0.11
Duration of rFSH administration (days) ^q	9.7±2.4	9.5±1.8	0.53
No. of follicles ≥ 12 mm (Mean±SE) ^q	20.8±4	20.3±3.3	0.43
No. of oocytes retrieved (Mean±SE) ^q	24.0±2.4	23.1±3.1	0.07
No. of MII oocytes (Mean±SE) ^q	16.22±8.0	15.99±7.8	0.83
No. of oocytes fertilized (Mean±SE) ^q	12.1±7.0	8.5±4.1	0.000*
No. of embryo transferred (Mean±SE) ^q	2.33±0.64	2.06±0.47	0.004*
Endometrial thickness at ET day (Mean±SE) ^q	8.8±1.4	9.4±1.6	0.01*
Hospital admission ^q	1	–	0.45
No. of Ascitis ^a cases n (%) ^q	49	15	0.000*
Without or mild OHSS n (%) ^q	20(28.9)	54(78.3)	0.000*
Moderate OHSS n (%) ^q	33(47.9)	14(20.3)	0.000*
Severe OHSS n (%) ^q	16(23.2)	1(1.4)	0.000*
Early OHSS n (%) ^q	49(100)	12(80)	0.08
Late OHSS n (%) ^q	–	3(20)	

Table 3 Comparison of body weight and blood parameters of moderate and severe cases of OHSS in two groups

Parameter	Moderate OHSS		P-value	Severe OHSS ^a	
	Albumin group (n=33)	Cabergoline group (n=14)		Albumin group (n=16)	Cabergoline group (n=1)
Day of oocyte retrieval					
Haemoglobin (g/dl)	13.2(1.0)	12.9(1.0)	0.28	13.5(0.92)	14.2
Haematocrit (%)	40.6(2.0)	38.8 (3.0)	0.1	41.1(2.7)	43.5
Leukocytes (n/mm ³)	8261.5(3148.4)	7995.3(3376.8)	0.25	8589.3(3295.2)	8850
Creatinine (mg/dl)	0.6(0.1)	0.5(0.2)	0.5	0.7(0.1)	0.7
Body weight (kg)	61.8 (10.3)	66.8 (11.1)	0.14	64.5(8.2)	46
7 days after oocyte retrieval					
Haemoglobin (g/dl)	13.3(1.2)	13.3(0.98)	0.74	14.4(0.81)	15.5
Haematocrit (%)	40.1(3.3)	39.9(3.1)	0.51	43.5(2.7)	44.9
Leukocytes (n/mm ³)	8585.2(3045.2)	8017.8(3163.9)	0.4	1034.5(4350.4)	10300
Creatinine (mg/dl)	0.6(0.2)	0.6(0.1)	0.9	0.9(0.2)	0.8
Body weight (kg)	62.0(10.2)	67.1(11.0)	0.2	71 (9.3)	53

Values are mean (SD)

^a because numbers of severe cases in two groups weren't comparable, p value hasn't mentioned

the causes of infertility between the two groups so that the number of patients with male factor infertility in the Cb2 group was higher than HA group ($p=0.03$).

Although the mean total rFSH dose and duration of gonadotropin administration, total number of follicles ≥ 12 mm and retrieved oocytes were similar in both groups ($p=0.11$, $p=0.53$, $p=0.43$, $p=0.07$ respectively), as shown in Table 2, the number of fertilized oocytes and transferred embryos in the HA group was significantly higher than in the Cb2 group.

Follow-up of the patients showed that moderate OHSS was observed in 33 subjects in the HA group versus 14 cases in Cb2 group and severe OHSS cases were more common in the HA group than in the Cb2 group ($P<0.001$). The observations showed that patients with preventive treatment in both groups presented a significant reduction in the incidence of late OHSS. However, no significant difference was found between groups. All OHSS cases in the HA group were early onset OHSS ($p=0.08$). All the severe cases in our study were grade 4 of Golan et al. criteria and treated as outpatient. Only one case in the HA group was hospitalized with oliguria (urine output <400 cc per 24 h) and Haemo-concentration (hematocrit $>45\%$) (Table 2).

According to the Ordinal Logistic Regression model on OHSS incidence and severity, among different clinical parameters only, type of preventive drug was significant and had a predictive value on OHSS events in this series. The odds ratio for comparing preventive drugs is 1.1 with a confidence interval of 95% (0.3–4.5) ($p<0.001$). This means that the percentage of patients who have been treated with dostinex in the incidence of OHSS is less than in the albumin group.

Table 3 shows weight and blood parameters compared at oocyte retrieval and 7 days later in cases where OHSS

developed. No significant differences were found in any parameters studied among moderate cases between the two groups. The number of severe cases was not comparable and the P value hasn't Statistical values for the reporting.

Fertilization rates were higher in the HA group than in the Cb2 group, but the implantation, chemical and clinical pregnancy and multiple pregnancy rates as well as the number of miscarriages were similar in both groups (Table 4).

Discussion

The studies have shown the increase in vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR-2) mRNA expressions as the fundamental role in vascular hyper permeability and OHSS presentation related with

Table 4 IVF/ICSI outcomes between two groups

Variables ^a	HA (n=69)	Cb2 (n=69)	P-value
Fertilization rate (%) □	70	52	0.000*
Implantation rate (%) □	54	53	0.81
Chemical pregnancy rate n (%)	29 (43.4)	21(30.4)	0.18
Clinical pregnancy rate n (%)	26 (37.6)	20 (29)	0.33
Multiple pregnancy rate n (%)	5 (17.2)	3 (14.2)	0.5
First trimester miscarriages n (%)	3 (1.3)	1 (0.4)	0.37

^a Chi-square test

*Significant difference

human chorionic gonadotropin (HCG) injection in the patients undergoing ART [11, 12]. Dopamin agonists can inhibit phosphorylation of the receptor VEGFR-2 [12, 13]. Therefore they can reduce the vascular permeability and OHSS presentation in the ART cycles. Cabergoline (Cb2) has been studied with a decrease in the severity [14–16] or incidence [19] or both [20] of OHSS. Our results have proven that patients who took Cb2 manifested significant difference in the severity also incidence of OHSS presentation compared with those who took Human Albumin (HA). Our researches showed if Cb2 administration in the oocyte retrieval day minimized the severity and incidence of OHSS but the risk of this lethal disease had never been excluded.

Based on our research, we found one study with same subject, although several studies evaluate the efficacy of albumin or Cb2 alone or in compare to other methods. Soliman in a clinical trial study has been compared the efficacy of Cb2 alone, Cb2 plus i.v. albumin and i.v. albumin alone [17]. This study had a small sample size, 15 cases in each group, and concluded that it seems Cb2 alone is as effective as Cb2 plus i.v. albumin and both were more effective than i.v. albumin alone in the prevention of the early onset type of severe OHSS.

It is noteworthy that we compared two drugs with different preventive mechanisms; Albumin seems to have osmotic functions that draw extracellular fluid into the circulation and possesses transport functions, binding and inactivating the vasoactive intermediates responsible for the pathogenesis of OHSS. Our data and many of currently studies [5–9] support the suggestion that the intravenous albumin administration (20 gr in the day of oocyte retrieval) does not reduce the occurrence of severe OHSS. Our results showed that human albumin at this dose, hadn't any benefit effects on reduction the incidence of moderate OHSS too.

Our observations presented that the majority of OHSS in the two groups were early onset of OHSS, in contrast to the findings of Carizza et al. [15]; this is probably due to the lower pregnancy rate in our study (20–30% versus 40–50%).

Despite the lower number of fertilization in the Cb2 group, treatment in both groups resulted in a similar ongoing Pregnancy rate per started cycle therefore oral administration of Cb2 presented no adverse effect on ART outcome, in agreement with other previous studies [14–17].

Although the difference in the fertilization rate is statistically significant, the clinical evidence of this difference can be due to some heterogeneity in the causes of infertility in two groups undergoing Cb2 or IV albumin therapy. Investigators emphasize that a dopamine agonist can reduce the activity of the receptor VEGFR-2 without affecting luteal angiogenesis or any adverse effects on pregnancy outcome [14–17]. According to our findings, HA and Cb2 groups had similar other ART outcomes in terms of implantation and miscarriage rates. These results could confirm those investigators idea but it needs more evaluation.

Our estimation of the drug's cost determined that seven tablets of cabergoline are priced at half the price of two human albumin vials, which shows the cost-effectiveness of prophylactic administration of cabergoline for high-risk patients

Our study was not blinded because we have ethical limitations for using placebo for high risk patients; we suggest that other researchers if possible, perform blind randomized clinical trials by using a placebo tab to evaluate the efficacy and safety of different doses and durations of Cb2 administration.

Our results have demonstrated that administration of oral Cb2 was more effective than 20 g I.V albumin in prevention of OHSS in high risk patients.

Despite the more reduced number of OHSS after Cb2 usage than the other drug, a few more issues about how to diminish this disease thoroughly remain. If the time of the starting dose had been changed, a lower number of cases or none may have been developed to OHSS. There is a clinically important question about the best time of Cb2 usage for prevention of OHSS. Further studies can be designed to evaluate the more effective time of Cb2 administration either in the day of HCG injection or in the oocyte retrieval day.

Our estimation of drug's cost determined that seven tablets of cabergoline are priced at half price of two human Albumin vials, which shows cost-effectiveness of prophylactic administration of cabergoline for high risk patients. No adverse effects have been reported for Cb2 in this study. This dose of drug seemed to be well-tolerated by our sample population

In conclusion, prophylactic low dose oral administration of Cb2 decreases the incidence and severity of OHSS higher than HA. Additionally, Cb2 administration for patients is less costly and safer than IV administration of HA. However, further well designed studies especially about the best time and dose for the drug administration are needed.

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