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EFFECT OF DOPAMINE AGONIST (BROMOCRIPTINE MESYLATE) VS HUMAN ALBUMIN FOR PREVENTION OF OVARIAN HYPERSTIMULATION SYNDROME(OHSS)

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ABSTRACT

OBJECTIVE: *To compare the effectiveness of Bromocriptine Mesylate (1.25mg) Vs human albumin (50ml) in patients who were at high risk of Ovarian Hyper-stimulation Syndrome (OHSS)*
STUDY DESIGN: *comparative study.*
PLACE AND DURATION OF STUDY: *Baqai institute of Reproduction and developmental Sciences (BIRDS) from January 2008 till December 2009.*
METHODOLOGY: 6*0 women who were at high risk of OHSS were selected for prophylaxis of OHSS. 30 women (group 1) were given oral bromocriptine mesylate in a dose of 1.25 mg started from day of ovum pick up at bed time for 7 days and rest 30 women (group 2) received 50 ml human albumin infusion at time of oocyte retrieval and embryo transfer for prophylaxis of OHSS as a standard treatment. Follow up of all these women were done. Any woman who presented with sign/symptoms, suspected of OHSS was hospitalized for further observation and management.*
RESULTS: *Age range of women was 20 – 35 years and a mean age of 27.5 years. High risk factors for OHSS in both groups were detected. In group 1, PCO was found in 20 (66.6%) women. 1 (3.33%) woman was of young age (<22years). Low BMI (<18) was seen in 1(3.33%) woman .History of OHSS in previous ICSI cycle was found in 1 (3.33%) .Increased sensitivity to gonadotropins as an individual,s response was seen in 4 (13.33%) .Day 3 FSH < 7 IU/L was found in 3(10%) women .While in group 2 , 21(70%) women had PCO , 1(3.33%) woman was of young age ,1 (3.33%) woman had BMI < 18 .Increased sensitivity to gonadotropins was found in 4 (13.33%) women. Day 3 FSH < 7 IU /L was found in 3(10%) women. In group 1 ,mild OHSS was found in 13.33% women and moderate in 3.33% women .No woman had severe OHSS. While in group 2 , mild OHSS was seen in 43.33% women ,moderate in 20% and severe in 3.33% women.*
CONCLUSION: *Bromocriptine in low doses was found effective for prevention of OHSS as compare to human albumin infusion in studied sample.*

KEY WORDS: Bromocriptine, Ovarian Hyperstimulation Syndrome,Gonadotropins.

INTRODUCTION:
Ovarian hyperstimulation syndrome (OHSS) is defined as shift of serum from the intravascular space to the third space and mainly to the abdominal cavity that occurs when the ovaries become enlarged due to follicular stimulation [1]. Typically , OHSS is a complication of ovarian stimulation by gonadotropins used for invitrofertilization (IVF) followed by the administration of human chorionic gonadotropins (HCG) to trigger the final steps of oocyte maturation [1] .It is commonly seen when a stronge ovarian response occurs , characterized by the

Authors contribution
Dr Sajida Parveen designed and wrote the manuscript .Dr Majida Khanum helped in statistical analysis.Dr Peter Bailie has supervised the study. Dr Shehnaz Hassan has reviewed before submission of manuscript.
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TABLE 1
COMPARISON OF RISK FACTORS FOR OHSS IN BOTH GROUPS

Risk factors for OHSS	Group I	Group II
Observations	N=30	N=30
PCO Young age of women	20 (66.6%) 1 (3.3%)	21 (70%) 1 (3.3%)
Low BMI	1 (3.3%)	1 (3.3%)
History of OHSS in previous ICSI cycle	(3.3%)	0
Increase sensitivity to gonadotropins	4 (13.33%)	4 (13.3%)
Day 3 FSH <7 IU /L	3 (10%)	3 (10%)

TABLE 2
COMPARISON OF SEVERITY OF OHSS IN BOTH GROUPS.

Severity of OHSS	Group 1	Group 2	
	N=30	N=30	P - Value
Mild	4 (13.3%)	13 (43.3%)	0.010
Moderate	1 (3.3%)	6 (20%)	0.044
Severe	0	1 (3.3%)	0.313

development of large number of follicles , high serum estradiol (E2) level and enlarged ovaries[2]

Three grades of OHSS can be distinguished by clinical and Sonographic criteria[3] .Mild ,Moderate or Severe . Mild is subdivided in to two grades .Features of grade 1 are abdominal distention and discomfort .Grade 2 includes Features of grade 1 plus nausea , vomiting and / or diarrhea , ovarian enlargement may be up to 5 - 12 cm. Moderate , grade 3 , constitute of features of mild OHSS and sonographic evidence of ascites .While in severe grade 4 form , features of moderate OHSS are present with clinical evidence of ascites and / or hydrothorax or respiratory compromise . In severe grade 5 , along with all the above features other parameters which are included are hypovolemia , hemoconcentration , coagulation abnormalities or diminished renal perfusion and function.[3]

In severe forms, renal failure and reduced perfusion to vital organs , such as brain and heart may lead to coma and death.[4] The mortality rate has been estimated between 1 in 45,000 and 1 in 500,0005. Individual ,s susceptibility may be the consequence of increased ovarian sensitivity to gonadotropins.[6] Increased sensitivity has been well documented in women with polycystic ovaries (PCO) , of young age , with low body mass index (BMI) and day 3 FSH level < 7 IU/L.[6,7] There is now a general consensus that women with ovaries primed with follicular stimulating hormone leutinizing hormone and subsequently exposed to human chorionic gonadotropin develop a picture in which the ultimate pathophysiological step is increased vascular permeability (VP).[8]

Recent observation from animal studies suggest that vascular endothelial growth factor (VEGF) , plays a pivotal role in increasing VP.9 OHSS may be early or late form.10 Studies have shown that VEGF , a normal product of ovary plays a critical role in the early process of ovarian hyper stimulation syndrome .10 The hypothesis that low doses of dopamine r2 activiting drugs are capable of decreasing VP , by inhibition of VEGF without affecting angiogenesis of pregnancy was tested in context of OHSS in rodents and humans.[11]

Bromocriptine mesylate (parlodel) is an ergot derivative with potent dopamine receptor agonist activity . Each parlodel tablet for oral administration contains 2.5mg bromocriptine mesylate . The objective of study was to compare the effect of low doses of bromocriptine mesylate (1.25mg) with human albumin (50ml) which is given as standard treatment, for prevention of early forms of OHSS , in women who had ovarian stimulation by gonadotropins

TABLE 3
CLINICAL , BIOCHEMICAL , METABOLIC , HEMATOLOGICAL , AND SONOGRAPHIC PROFILE OF WOMEN WHO DEVELOPED OHSS IN BOTH GROUPS.

Parameters	Group 1 (n = 30)	Group 2 (n = 30)	P - Value
	N (n%)	N (n%)	
Abdominal distention and discomfort	4 (13.3%)	13 (43.3%)	0.01
Nausea, vomiting and/ or diarrhea	4 (13.3%)	13 (43.3%)	0.01
Respiratory compromise or hydrothorax	0	1(3.3%)	0.313
Oliguria	0	0	****
Electrolyte imbalance	0	0	****
Hemoconcentration[a]	0	0	****
Renal dysfunction[b]	0	0	****
Liver dysfunction[c]	0	0	****
Sonographic evidence of			
Ovarian enlargement between 5-12cm	4 (13.3%)	13 (43.3%)	0.01
Ascites >9 cm^2	2 (6.6%)	6 (20%)	0.129

Hematocrit greater than 45%.
Creatinine greater than 1.2mg/dl
[c]Asparate transaminase or Alanine transaminase greater than 40U/ml

for Intracytoplasmic sperm injection (ICSI) and had a risk of OHSS.
Local search does not provide us any research on this important issue related to assisted reproduction.

SUBJECT AND METHODS:
This comparative study was conducted at Baqai Institute of Reproduction and developmental sciences (BIRDS) during a period of January 2008 till December 2009. A total of 255 women were booked for ICSI during this period. Only women at risk of OHSS, were included in this study. Inclusion criteria was , women who developed >8-10 follicle of different sizes in each ovary as a result of controlled ovarian stimulation (COS). E2 level >3500-4000 pg / ml , retrievel of 20 or more oocytes on ovum pick up. Only 60 women fulfilled this criteria , were selected for prophylaxis of OHSS.
Rest of women were excluded from this study. To all those women who were selected for this study ,down regulation of ovaries was done by gonadotropic releasing hormone (GnRH) agonist from day 21 of preceding cycle .[7] Ovarian stimulation was started from day 2 of menstrual cycle with low dose of recombinant follicular stimulating hormone(FSH) and / or pure human menopausal gonadotropin (HMG) . Follicular tracking was done by serial transvaginal ultrasound . Serial monitoring of serum E2 level was done in all selected women .[12] HCG was given when 3 or 4 mature follicle were seen in each ovary. Ovum pick up was performed 34 to 36 hours after HCG. All wpmen included in this study , were assigned into two groups . Consecutive sampling method was followed for all selected women .In group 1, 30 women were given oral bromocriptine mesylate in a dose of 1.25 mg at bed time from ovum pick up for 7 days .While in group 2 , equal number of women received 50 ml of intravenous human albumin at time of oocyte retrievel and embryo transfer for prophylaxis of OHSS as a standard treatment.[5]
Embryo transfer (ET) was done 2 0r 3 days following ovum pick up. On day of ET , all women were assessed clinically , to suspect early onset OHSS. A routine ultrasound was done to all women for ovarian size and presence of fluid in abdominal cavity. After ET all women were sent home with a general advice of rest , oral analgesics and progesterone vaginal pessaries. Follow up of all these women was done by telephone after 2 or 3 days of ET Any woman who complained of vomiting abdominal pain or distention was hospitalized
for further observation and management ,which included more potent
analgesic , antiemetics , intravenous fluids and regular monitoring of vitals , weight , urine output , abdominal girth , regular sonogram for size of ovary and frequent serial laboratory determinations of electrolytes , hematocrit , renal function and liver function test .[13]
Both groups were compared by Chi-square test and SPSS V.15 was used for data analysis.Results of both the groups are summarized below.

RESULTS:
A total of 60 women were included in this study which were divided
in two equal groups .Age ranging from 20 - 35 years and a mean age of 27.5 years .High risk factors for OHSS were detected in both groups . In group 1 ,polycystic ovarian syndrome (PCOS) was found in 20 (66.6%) women .1 (3.33%)

woman was of young age (<22years) . Low BMI (<18) was seen in 1(3.33%) woman .History of OHSS in previous ICSI cycle was found in 1 (3.33%) .Increased sensitivity to gonadotropins as an individual,s response was seen in 4 (13.33%) .Day 3 FSH < 7 IU/L was found in 3(10%) women .While in group 2 , 21(70%) women had PCOS , 1(3.33%) woman was of young age ,1 (3.33%) woman had BMI < 18 .Increased sensitivity to gonadotropins was found in 4 (13.33%) women. Day 3 FSH < 7 IU /L was found in 3(10%) women. (Table 1)

In group 1 , mild OHSS was found in 4 (13.3%) women and moderate OHSS in 1 (3.33%) women . 24 (80%) women remained well on bromocriptine .All these women ,who developed mild or moderate OHSS were hospitalized . .No case of severe OHSS was observed in group 1.In group 2, 13 (43.33%) women developed mild OHSS ,6 (20%) women developed moderate OHSS and 1(3.33%) women developed severe OHSS. (Table 2)

Clinical, biochemical, hematological, metabolic and sonographic markers were observed in both groups , who developed mild , moderate or severe OHSS in this study (Table-3).

DISCUSSION:

The importance of OHSS as a serious complication of ovulation induction and the need for finding a new drug for preventive measures is well recognized now. In past , several methods were tried to prevent OHSS , however , the syndrome was unlikely to be eliminated completely Reduced HCG dose , coasting , embryo cryopreservation , albumin , corticosteroids and mild protocols are still being used to ovoid OHSS[14]. However , it is done at expense of cancellation of cycle. Intravenous albumin and cryopreservation of all embryos for transfer in later cycle were not effective in prevention of OHSS[14].

In a country like Pakistan , where socioeconomic conditions of individuals are considered as an important issue .Cancellation of IVF or ICSI cycle of those , who are at risk of OHSS , seems difficult , so there was urgent need to work on a drug that should be safe cheap and effective for prevention of OHSS.

Basu et al15 has shown that , the neurotransmitter dopamine strongly and selectively inhibits the VP and activity of VEGF. It seems logical that if we can antagonize or limit the production of VEGF , we may be able to prevent OHSS or atleast reduce its severity .16 This was the basis of our study also. At present, we feel that the most difficult clinical challenge is to correctly predict patients at high risk for OHSS. Day 3 FSH level ,Patients age , E 2 peak value , number of follicles or oocytes retrieved and presence / absence of PCO ,all show a suboptimal sensitivity to predict OHSS development[17] Although , prediction of high risk individuals and determination of high risk factors for development of OHSS before start of prophylaxis is more suitable ,as seen in our study. In our study PCO was the most common risk factor observed in both groups. Women affected by PCO , are at high risk of OHSS with an incidence of 6% in these women as compared to 1% of general infertile population after controlled ovarian stimulation .[18]

In our study day 3 FSH < 7mIU / ml was observed in 10% population in both groups . Barmat et al ,observed 95% of severe OHSS developed in patients with 3rd day FSH <7mIU / ml7. Ovarian hypersensitivity to gonadotropins was observed in 13.3% women in our study which is considered to be the consequence of mutations in FSH receptors[19].

In our study 30 women were given bromocriptine for prophylaxis of OHSS from evening of pick up in group 1. similarly Manno et al 20 began administrating Cabergoline at a dose of .5mg /24 hours on the evening after pick up, to 20 patients at risk of hyperstimulation.They reported an absence of OHSS and a prompt improvement in hospitalized patients[20]. Gomez et al [21] used Bromocriptine for down regulation of hyperstimulated ovaries revealed dopamine agonist Bromocriptine as an effective and specific method to block increased VP in OHSS.

In group 2 of our study 30 women were given human albumin for prophylaxis of OHSS, out of these 30, 6 (20%) women developed ascites >9 cm 2 . 1(3.33%) woman developed hydrothorax and Clinical ascites. Hepatic and renal functions were not altered in this group.

Doldi et al [22] demonstrated that albumin may be useful to increase the intravascular volume of OHSS patients , without a concomitant reduction in vascular permeability ,however its effect on intravascular volume and hematocrit may be of short duration .Cost and hypersensitivity risks associated with albumin administration can not be overlooked also. Bellver j et al [23] reported that albumin administration has no effect on OHSS development.

In our study , clinical , biochemical , hematological and sonographic Parameters were observed for detection of severity of OHSS in both groups. None of these markers were dangerously elevated in group 1. No evidence of Oliguria , respiratory difficulties , deranged hematocrit electrolyte imbalance , renal and liver difficulties were found in this group. Similar results were presented by Fabreques et al [24] by giving 0.5mg / day cabergoline for prevention of OHSS in high risk patients. They measured hematocrit , hemoglobin and leukocyte concentrarion as biological markers of hemoconcentration which was considered to be the Best indicator of severity of OHSS.

In general , mild forms of OHSS constitute around 20 -30% of IVF cycles, moderate 3-6 % of cycle and severe forms 0.1-0.2% of cycles[25]. But in our study ,in group 1, mild OHSS was found in only 13.3% women and moderate in 3.33%. No case of severe OHSS was seen. While in group 2, mild OHSS was found in 43.33% ,moderate in 20% and severe in 1% women. In our study P value was < 0.05 for mild and moderate OHSS which is considered as significant but as it was >0.05 for severe OHSS ,so for severe OHSS only null hypothesis applies which shows no difference in the efficacy of both drugs for prophylaxis of severe OHSS.

Small sample size , was the major limitation of this study. In this study Bromocriptine was started in low doses from day of ovum pick up but more research and large trials are necessary for safe doses , timing , when to start Bromocriptine i.e from day of pick up or HCG , duration of therapy and its effect on late onset OHSS and pregnancy rates , as well , need to be investigated further , in order to ovoid preventable deaths and to make Assisted Reproduction more safer all over the world.

CONCLUSION:

we observed that Bromocriptine (Parlodel) in low doses was found effective for prevention of mild and moderate OHSS in studied women but large trails are necessary in order to include this drug as part of standard treatment.

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