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# Comparing the mannitol and albumin in management of the severe ovarian hyperstimulation syndrome (OHSS), a randomized clinical trial, with cost-effectiveness analysis

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**ABSTRACT**

**Background:** Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication including pleural effusion, acute renal insufficiency, and venous thromboembolism associated with controlled ovarian stimulation during assisted reproductive technology. A number of clinical studies have reported on the use of plasma expanders such as albumin, hydroxyethyl starch (HES), mannitol, polygeline, and dextran as a possible intervention for the prevention of OHSS.
**Objective:** The purpose of this study was comparing the efficacy and cost-effectiveness of mannitol rather than albumin for the treatment of severe OHSS.
**Materials and Methods:** We conducted a single-center and comparative randomized clinical trial with two parallel patient groups. 47 patients with severe OHSS were selected with inclusion criteria.
In the albumin group (n=26), patients received 100 g/day intravenous albumin. Mannitol therapy (n=21) started twice a day using 100 gr mannitol infusion over 4 hours. Patients were monitored according to the standard protocol. Statistical analysis will be performed to analyze and compare the data between two groups in order to determine the efficacy (based on the abdominal circumference, intake/output of fluid, correction of blood electrolytes), side effects, and cost of drug therapy between the two treatment modalities.
**Results:** The efficacy of drug therapy was evaluated by examining the results of daily urine output, serum biochemistry analytes, weight, and abdominal circumference in both groups. There were no significant differences between the two study groups in terms of patient age, clinical signs and symptoms, and laboratory findings such as hematocrit, creatinine, potassium, fluid intake/output, weight, and abdominal size. Significant improvement of OHSS syndrome was observed in patients using mannitol which no patient has reported any side effects such as respiratory distress syndrome, renal failure, or thromboembolism. In the albumin group, 15.38 % of patients presented with acute respiratory distress syndrome (ARDS). Another outcome of this study was the significant economic difference between the two managements of severe ovarian hyperstimulation syndrome. Mannitol therapy was obviously cost-effective versus albumin therapy.
**Conclusion:** The use of mannitol is comparable and superior to albumin for the treatment of severe OHSS with regard to the protective effect against the occurrence of acute respiratory distress syndrome. Base on this study, its cost-effectiveness makes mannitol an ideal drug for OHSS treatment. This study suggests that mannitol can be first-line therapy for the treatment of severe OHSS, therefore, the addition of mannitol as a treatment of ovarian hyperstimulation syndrome is recommended in the drug pharmacopeia.

**Keywords:** Ovarian Hyperstimulation Syndrome (OHSS), Mannitol, Albumin, Efficacy, Side Effect, Cost-effectiveness.

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## Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of assisted reproduction techniques (ART), which can occur following controlled ovarian hyperstimulation and after the injection of human chorionic gonadotropin (HCG) [1]. The reported prevalence of the severe form of OHSS is small, ranging from 0.5 to 5% [2]. Due to leakage of fluid through the impaired blood vessels both within and outside the ovary, there is a massive fluid shift from the intravascular space to the third compartment, that results in intravascular hypovolemia with concomitant development of edema, ascites, hydrothorax, and/or hydropericardium [3]. Severe OHSS can lead to serious and potentially life-threatening complications, including pleural effusion, acute renal insufficiency, and venous thromboembolism [4]. Extravasation of fluid and resultant renal dysfunction resulting from decreased perfusion leads to oliguria. Increased reabsorption of sodium and water which occurs in the proximal tubule, leads to low urinary sodium excretion [5]. The exchange of hydrogen and potassium for sodium in the distal tubule is reduced causing, hyperkalemia and a tendency to develop acidosis. The hypovolemia of OHSS leads to hemoconcentration and creates a hypercoagulable state [6].

The main goal of treatment is maintaining circulatory volume and electrolyte balance [7]. Efforts should be directed toward restoring a normal intravascular volume and preserving adequate renal function. This may be achieved by using colloid plasma expanders [8]. A number of clinical studies with conflicting results have reported on the use of plasma expanders such as albumin, hydroxyethyl starch (HES), and mannitol as a possible intervention for the treatment of OHSS [7,9–11]. The ideal colloid solution for the treatment of patients with severe OHSS is still unknown [10]. Human albumin protein, however, is considered the most physiologic solution for this purpose. It may act by binding and inactivating substances implicated in the pathogenesis of OHSS, such as vascular endothelial growth factor [12–14], or by increasing the colloid oncotic pressure of the plasma, thus drawing fluid from the third compartment [13]. It is an animal product and its supply worldwide is faced with limitations including difficult production process high cost, allergic reactions, and virus/prion transmission [7,15].

Mannitol is a sugar alcohol [16,17] that works as an osmotic diuretic [18]. It causes osmotic diuresis by increasing the osmotic pressure in the glomerular filtrate and preventing water and electrolyte reabsorption. Infusion of mannitol is approved for controlling increased intracranial pressure in brain edema, increased intraocular pressure (IOP), and the stimulation of the urinary excretion of certain toxins [11,18]. In addition, mannitol has been promoted as a renal protective agent in patients at high risk of developing renal failure, such as those undergoing cardiac and vascular surgery, renal transplantation, and in patients with jaundice and rhabdomyolysis [18]. Former publications reported a benefit of prophylactic administration of mannitol before and immediately after oocyte retrieval in women at high risk for severe OHSS [16]. In this novel study, we compared the safety, efficacy, and cost-effectiveness of albumin vs. mannitol therapy in the management of severe ovarian hyperstimulation syndrome (OHSS) patients.

## Material and Methods

This study is a controlled clinical trial was performed in the Sarem Women's Hospital (Tehran, Iran). In this trial, 47 patients (24 to 40 years old) with severe ovarian hyperstimulation syndrome (OHSS) admitted to the hospital by the presence of rapid weight gain, tense ascites, hemodynamic instability, respiratory difficulty, progressive oliguria (<300mL/d or <30mL/h), and laboratory abnormalities including hematocrit>48%, hyponatremia (<135mEq/l), hyperkalemia (>5.0mEq/l), and elevated creatinine (>1.2mg/dl). They divided randomly into two parallel groups that treated with albumin or mannitol (Figure 1). Exclusion criteria were patient reluctance and no cooperation, intolerance to treatment, or exacerbation of symptoms. In the albumin group, 26 patients received 100 g/day intravenous albumin (OCTAPHARMA AG, Switzerland) over 4 hours. In the mannitol group, 21 patients received an intravenous infusion of 100 gr mannitol over 4 hours, twice a day. Rapid initial hydration by 500 ml of normal saline 0.9% and then 30 ml/kg/day, by intravenous intake, perform for both groups. Careful clinical monitoring and evaluation of the drug dose during infusion, electrolyte control and correction (if necessary), and maintaining a serum osmolality less 300-320 mOsm/kg are also considered to minimize the side effects of the drugs. Patients in both treatment groups and statistical analysts were unaware of the type of medications (a double-blind study). The efficacy of the study medications was compared between the two groups in terms of routine vital signs, abdominal examinations, pulmonary auscultation, and measurement of abdominal circumference, patient's weight, diuresis, serum biochemistry, and fluid intake/output. In addition, complications such as acute renal failure, acute respiratory distress syndrome, and thromboembolism were investigated in two groups. Also, a cost-effectiveness analysis was performed in albumin and mannitol therapy groups. Finally, the data of the study were analyzed by descriptive and analytical statistics using IBM SPSS software (Version 25, IBM Corp., Armonk, N.Y., USA). Kolmogorov-Smirnov statistical test was used to determine the normal distribution of quantitative data. Due to the non-normal distribution of data, the nonparametric Mann-Whitney U test was used to compare the means, and also for the qualitative data, Fisher's exact test was used. For the analysis of the results, the principle of "intention to treat" is used.

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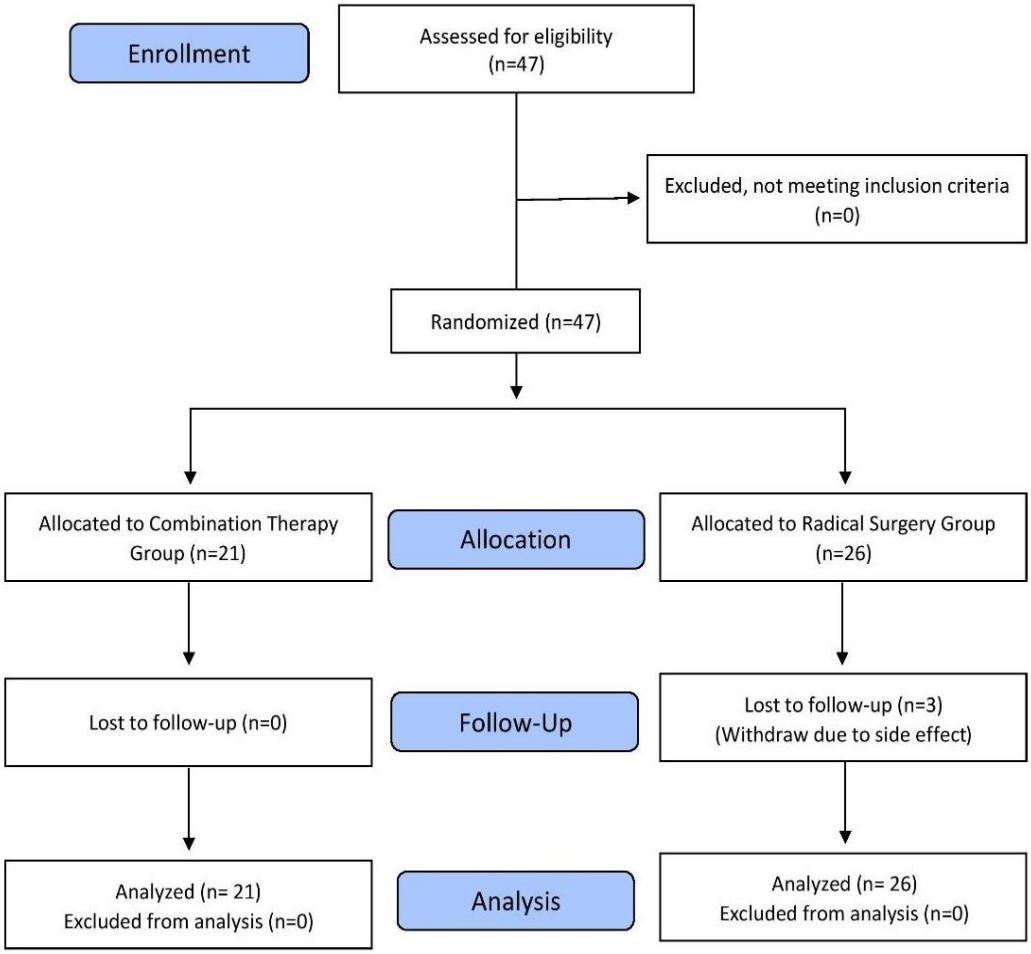


Figure 1. Study flow diagram (CONSORT 2010), Intention to treat (ITT) approach

## Results

In this study, the overall results of treatment of OHSS patients with mannitol in comparison with albumin therapy in severe cases of OHSS, including efficacy, side effects, and costs were analyzed. The mean age of patients in the albumin group was 31.69 years and in the mannitol group was 32.52 which is not a significant difference between them (*PV>0.05*). The efficacy of drug therapy was evaluated by examining the results of daily urine output, serum biochemistry analytes, vital signs, weight, and abdominal circumference. There was no significant difference in clinical signs and symptoms including heart rate, respiration rate, body temperature, weight, and abdominal circumference between the two study groups (*PV>0.05*). Also, some laboratory findings including hemoglobin, hematocrit, creatinine, blood urea nitrogen, blood sugar, and potassium were not significantly different between the two study groups (P>0.05), while blood sodium and osmolality were significantly lower in the mannitol group (P<0.05) (Table 1). There was an obvious improvement in the general condition of patients taking mannitol versus albumin. Mean daily urinary excretion was significantly higher in the mannitol therapy group than the albumin group (*P<0.05*); however, since fluid intake in the mannitol group was higher, the ratio of fluid intake to urinary excretion was higher in the mannitol group, which was not significant (*P>0.05*). Correction of oliguria/anuria and urinary output process, as an indicator of renal function and patient recovery, was significant in the mannitol group (Table 1).

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Table 1. Comparison of parameters in the albumin and the mannitol therapy groups[1]

| Parameter | Albumin Group (n = 26) Mean ± SD | Mannitol Group (n = 21) Mean ± SD | Mean Difference | P-Value |
|---|---|---|---|---|
| Age | 31.69 ± 4.5 | 32.52 ± 3.8 | 0.83 | 0.51 |
| Vital Signs | | | | |
| Pulse Rate (bpm) | 84.85 ± 8.6 | 84.62 ± 8.1 | -0.22 | 0.92 |
| Respiratory Rate (bpm) | 19.08 ± 1.5 | 18.10 ± 0.9 | -0.98 | 0.06 |
| Temperature (°C) | 36.88 ± 0.3 | 36.86 ± 0.2 | -0.02 | 0.79 |
| Weight (kg) | 69.27 ± 11.8 | 67.97 ± 13.0 | 1.30 | 0.21 |
| Abdominal Circumference (cm) | 95.15 ± 11.5 | 94.01 ± 12.2 | -1.15 | 0.74 |
| Blood Biochemistry | | | | |
| Hematocrit (%) | 35.07 ± 5.0 | 36.23 ± 5.3 | 1.15 | 0.53 |
| Hemoglobin (g/dl) | 11.60 ± 1.9 | 12.07 ± 2.0 | 0.47 | 0.59 |
| Creatinine (mg/dl) | 0.80 ± 0.1 | 0.84 ± 0.2 | 0.03 | 0.45 |
| Blood Urea Nitrogen (mg/dl) | 11.08 ± 4.3 | 9.00 ± 3.0 | -2.08 | 0.07 |
| Blood Sugar (mg/dl) | 94.42 ± 31.5 | 95.95 ± 25.3 | 1.52 | 0.85 |
| Sodium (mEq/l)2 | 136.04 ± 2.3 | 132.14 ± 3.8 | -3.89 | 0.00 |
| Potassium (mEq/l) | 4.13 ± 0.4 | 4.14 ± 0.3 | 0.01 | 0.92 |
| Osmolality (mOsm/kg) | 289.29 ± 5.3 | 269.26 ± 2.7 | -20.03 | 0.00 |
| Fluid Output, Daily (ml)[2] | 1905.76±99.5 | 3027.62±144.2 | 1121.86 | 0.00 |
| Δ of Fluid Intake-Output (ml) | -141.81± 37.9 | -194.25± 47.8 | -52.44 | 0.52 |

[1] The non-parametric statistical test, Mann-Whitney U, was used.
[2] Significant statistical difference have been observed (P<0.05)

Seven cases (26.92%) in the albumin group experienced acute respiratory distress syndrome, while no cases were observed in the mannitol group, which was a statistically significant difference (PV<0.05). However, no complication of renal failure and thromboembolism was seen in the two groups (Table 2).

Table 2. Comparison of adverse effects in the albumin and the mannitol therapy groups[1]

| Parameter | Albumin Group (n = 26) Number (%) | Mannitol Group (n = 21) Number (%) | P-Value |
|---|---|---|---|
| Acute Respiratory Distress Syndrome[2] | 7 (26.92%) | 0 (0.00%) | 0.01 |
| Renal Failure | 0 (0.00%) | 0 (0.00%) | 1 |
| Thromboembolism | 0 (0.00%) | 0 (0.00%) | 1 |

[1] The Fisher's exact test, was used.
[2] Significant statistical difference have been observed (P<0.05)

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In the cost-effectiveness analysis, the average cost of the drug for treatment with albumin was about 37 million riyals, this cost for mannitol was about one million riyals, which was a statistically significant difference (P<0.05). On the other hand, the duration of hospitalization in the treatment groups was not significantly different (P> 0.05) (Table 3).

Table 3. Comparison of drug cost and hospitalization in the albumin and the mannitol therapy groups[1]

| Parameter | Albumin Group (n = 26) | Mannitol Group (n = 21) | Mean Difference | P-Value |
|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | | |
| Drug Cost (IRR)[2] | 37,218,641 ± 558,005 | 1,050,000 ± 46,426 | -36,213,461 | 0.00 |
| Hospitalization (Day) | 4.04 ± 1.3 | 4.76 ± 1.5 | 0.72 | 0.41 |

[1] The non-parametric statistical test, Mann-Whitney U, was used.
[2] Significant statistical difference have been observed (P<0.05)

## Discussion

Ovarian hyperstimulation syndrome (OHSS) is a well-known complication of controlled ovarian stimulation during the process of assisted reproductive techniques, which can be fatal if not prevented or treated promptly in severe cases[3]. Ideally, women at risk for this disorder should be identified prior to stimulation, and stimulation protocols should be selected that minimize the risk of OHSS. Short-term protocols are currently routinely performed using gonadotropin-releasing hormone (GnRH) antagonists to prevent premature release of luteinizing hormone (LH). For the final maturation and release of the egg, a gonadotropin-releasing hormone agonist is used, which in some cases is accompanied by a low dose of human chorionic gonadotropin (hCG)[19]. If OHSS prevention strategies are not effective and the patient experiences severe OHSS, supportive care, paracentesis, and volume expander are recommended[15]. Clinical findings can be seen in various organs, and as the disease progresses, more organs become involved[20]. 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 [21]. Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, has emerged as one of the mediators intrinsic to the development of OHSS[21–23]. Pulmonary findings include pleural effusion, restrictive lung disease from ascites or paralytic ileus, and acute respiratory distress syndrome (ARDS). Cardiovascular findings include decreased intravascular volume, decreased blood pressure, decreased central venous perfusion, and compensatory increased heart rate and cardiac output with arterial vasodilation. Coagulation abnormalities include hemoconcentration and increased estrogen level that leading to hypercoagulability, and thrombosis[24–26]. The most abnormal plasma electrolytes findings in OHSS are hyponatremia and hyperkalemia caused by the depletion of body fluid volume and imbalance electrolytes in the urine[25,27].

Albumin has been widely used in the treatment of OHSS in high-risk patients[9,15,19,28–30], yet there is a lack of consensus regarding the benefits of its use and how its preventive mechanism acts[31]. In addition, there is some concern about the potential transmission of prions and viral infections such as Creutzfeldt-Jakob disease (CJD), hepatitis B and C, and human immunodeficiency virus (HIV)[32].

Mannitol has been applied as a renal protective agent in patients at high risk of developing renal failure, such as those undergoing cardiac and vascular surgery, renal transplantation, and in patients with jaundice and rhabdomyolysis[33–36]. Mannitol is a high hydrophilic sugar alcohol that is filtered at the glomerulus but not reabsorbed from the renal tubule. Mannitol is an osmotic diuretic widely used to reduce intracranial and intraocular pressures because of its osmotic diuretic action and presumed antioxidant properties[37]. It exerts osmotic activity within the proximal convoluted tubule and the descending limb of Henle's loop, limiting passive tubular reabsorption of water[38]. Mannitol also causes the release of renal prostaglandins that lead to renal vasodilation and an increase in urine flow[39]. Mannitol inhibits the reabsorption of sodium in the renal tubule, leading to a reduction of sodium that causes hypernatremia and hypokalemia[40]. These side effects could be beneficial in OHSS treatment as it is characterized by hyponatremia and hyperkalemia[41].

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In previous articles, we demonstrated the therapeutic efficacy and preventive role of mannitol in ovarian hyperstimulation syndrome[11,16,30,41]. The present study was performed to compare the efficacy and side effects of mannitol treatment with conventional albumin therapy in a controlled clinical trial. Also in this study, drug cost and length of stay (LOS) in hospital in both treatments were compared.

This study showed that the use of mannitol in the management of severe cases of ovarian hyperstimulation syndrome has an effective role and in terms of effectiveness is equivalent to the use of conventional albumin therapy. Mannitol was able to regulate urine flow, as an indicator of kidney function, and eliminate oliguria or anuria in these patients. Mannitol also improved blood biochemical parameters including hematocrit, hemoglobin, creatinine, urea nitrogen, sugar, sodium, potassium, and osmolality to an acceptable level, and clinical signs and symptoms such as vital signs, weight, and abdominal circumference were significantly improved in patients.

In this study, about 26% of patients treated with albumin did not respond completely to treatment and developed respiratory distress, while all patients treated with mannitol underwent treatment without any particular side effects. They were discharged in good general condition. On the other hand, the length of hospitalization of patients in both treatments was similar, but the cost of medication in the albumin group therapy was much higher than the mannitol group treatment, which is more than 35 times.

According to the findings of this study, due to the similar efficacy in both treatment regimens and fewer side effects in the treatment with mannitol than albumin, the use of mannitol in the management of severe cases of ovarian hyperstimulation syndrome, in terms of cost-effectiveness, is very remarkable and impressive.

## Conclusion

Cost-effectiveness is one of the important factors in choosing and applying a treatment regimen. This study showed that the use of mannitol in the management of severe cases of ovarian hyperstimulation syndrome is not only as effective as conventional albumin therapy but also has significantly fewer side effects. On the other hand, the 35-fold cost of using albumin compared to mannitol clearly makes the use of mannitol instead of albumin in the prevention and treatment of ovarian hyperstimulation syndrome reasonable and advisable.

## Suggestion

This study shows that mannitol can be the first line of treatment for the management of ovarian hyperstimulation syndrome, so the addition of mannitol as a treatment for ovarian hyperstimulation syndrome is recommended in pharmacopeia.

## Conflict of interest

There was no conflict of interest in this study.

## Ethics

The study protocol was approved by the ‘Research and Ethics Committee’ of Sarem Fertility and Infertility Research Center. Ethical approval of this trial was obtained from the ethics committee of Iran University of Medical Sciences (IRCT Number: IRCT20180305038953N1; Registered on 2018-05-15).

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