Use of Mannitol Therapy for Ovarian Hyperstimulation Syndrome (OHSS) Management

AboTaleb Saremi*, Maryam Namdar Khanzadeh, Maryam Shami, Fariba Mohammad Aliha, and Arash Pooladi
Sarem Fertility & Infertility Research Center (SAFIR), Sarem Women’s Hospital, Iran

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic and potentially fatal complication of assisted reproductive technologies (ART) that can occur following controlled ovarian hyperstimulation (COH) after the administration of human chorionic gonadotropin (hCG) [1]. OHSS may develop early or late after exposure to hCG, and is caused by endogenous hCG produced by the primary pregnancy; it may be more severe and more dangerous than the early form, and it is difficult to predict [2]. Whereas mild OHSS is of no clinical significance and does not require intervention, its severe form is difficult to control and treat, and is a life-threatening complication [3,4]. OHSS presents with the enlargement of the ovaries, ascites, hydrothorax, electrolyte

The prevalence of severe and moderate OHSS is reported to be 0.1% to 2% and 3% to 6% in the literature, respectively, but the prevalence increases to 38% or more in women in the high-risk group [1,2,8], which highlights the importance of detecting high-risk patients and adopting preventive measures in this group of patients. However, the risk of OHSS is always inherent, even in non-high-risk women [3]. Although prevention is the better strategy for the control of OHSS, the treatment and case management strategies for OHSS patients require focus, too. There have been a few non-effective (or questionable) choices for medical or nonmedical options for the treatment of OHSS [15,16-19]. However, albumin was expensive and not always available in Iran (due to an embargo); therefore, based on the pathophysiology of OHSS and the pharmacologic properties of mannitol, it was used as a replacement for albumin. Mannitol is a sugar alcohol [20], that works as an osmotic diuretic [21]. It causes osmotic diuresis by increasing the osmotic pressure in the glomerular filtrate and preventing water and electrolyte re-absorption. 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 [21].

Despite all of the significant advances in understanding the pathophysiology of OHSS, there is lack of information, and for this reason, OHSS prevention is the key approach for preventing OHSS-related morbidity and mortality [22,23]. Thus, we describe the management approach of OHSS with mannitol to investigate the effect of this drug on controlling OHSS.

MATERIALS AND METHODS

Study design and patient selection

The study was performed over a period of nearly 8 years, from April 2008 to February 2016, in the Sarem Women’s Hospital. The data were collected and analyzed using descriptive and analytical methods with SPSS version 23.

Due to the war, economic sanctions, and drug shortages, clinicians in the Sarem Medical Center had to replace albumin, which was expensive and difficult to find, with mannitol for a limited time because of its pharmacological properties.

To design a protocol for mannitol administration in OHSS, approved doses and methods in specific conditions (intracranial pressure [ICP], IOP) were followed [21]. For a comprehensive and credible administration method, the authors presented the primary satisfactory results of a compulsory primary pilot as evidence to the ethics committee of the medical center. After necessary evaluations and considering the safety of mannitol in the administered dose, the committee approved trying mannitol therapy for severe forms of OHSS on the conditions of observing the approved protocols and obtaining informed consent from the participants [approval number 3263-04, approval date: May 19, 1995]. After that, based on the 1-year pilot study of mannitol and the safety of this drug, the research group continued the use of mannitol for the management of OHSS. The data from the ensuing 20 years had been collected, but because of ovarian induction protocol changes, only the most recent 8 years’ data are used in this study. In this study all of the women were stimulated by the step-up and antagonist protocol especially in the high risk (e.g. PCOS) patients.

As mild OHSS requires no intervention [8,23], only patients with moderate and severe OHSS were included in the study. During the preparation of the patients for the IVF process and after ovarian stimulation, ultrasonic monitoring of the ovaries was performed in the infertility department. If a patient had the signs of moderate or severe OHSS despite prevention [8], she was entered into the study.

Patient monitoring and mannitol properties

During the treatment with mannitol, certain laboratory parameters and vital signs were evaluated, and clinical examinations were performed. The results were recorded in data registry forms on a daily basis to investigate the trend of the response to treatment, the complications of OHSS, and the side effects of mannitol.

The side effects of mannitol were closely monitored, and contraindications and warnings were considered. According to the medical literature, mannitol should not be used unless sufficient renal function and adequate urinary flow are ensured. It is suggested to evaluate the response of the kidneys after one or two doses. Careful clinical monitoring and evaluation of the drug dose during infusion, electrolyte control and correction (if necessary), and maintaining a serum osmolality less than 300 to 320 mOsm/kg are also recommended to minimize the side effects of the drug. Higher concentrations of mannitol; administering more than 200 g of mannitol per day; serum osmolality greater than 320 mOsm/kg or an osmolal gap greater than 50 mOsm/kg; concomitant use of other nephrotoxic drugs; sepsis; and underlying renal diseases increase the possibility of tubular necrosis or damage [21]. Moreover, mannitol infusion may result in electrolyte imbalance, dehydration, hypovolemia secondary to rapid diuresis, hyperglycemia, hypernatremia, hyponatremia, hyperosmolality-related hyperkalemia, metabolic acidosis, increased osmolar gap, and water intoxication [21]. These side effects, especially when overlapping with OHSS complications, demand more careful monitoring and follow-up. If patients experienced dyspnea, tachycardia, severe sweating, decreased output, or muscle cramps during mannitol therapy, a reduction in the dose of mannitol was considered. In patients receiving mannitol twice a day, we reduced the dose to once a day; in patients receiving one daily dose of mannitol, doses were withheld. To assess the risk of embolization in OHSS patients, plasma D-dimer measurement was added to the laboratory
Diuresis usually occurs 1 to 3 hours after mannitol infusion. The elimination half-life of mannitol is 4.7 hours. It has insignificant hepatic metabolism (to glycogen), and a urinary excretion of approximately 55% to 87% of the unchanged drug is recorded. Its distribution in the extracellular space is limited except in very high serum concentrations, and it cannot cross the blood-brain barrier [21].

The protocol of intravenous mannitol use

According to the Practice Committee of the American Society for Reproductive Medicine, the first priority in the management of OHSS is to correct hypovolemia, hypotension, and oliguria. (Note that all the patients with moderate and severe OHSS had a urinary catheter during mannitol therapy.) The committee recommends rapid hydration with intravenous fluids (500-1000 mL dextrose 5% and/or 0.9% saline) and careful monitoring of fluid intake during treatment to achieve adequate urine output (≥20-30 mL/h) and reverse hemoconcentration. Moreover, the guideline recommends 5% dextrose in normal saline (D5NS) rather than lactated Ringer’s solution, given the tendency of the latter to cause hyponatremia. The guideline points to mannitol as a plasma expander as well as albumin and fresh frozen plasma for the fluid management of OHSS patients [15].

1. Considering the dose of mannitol in increased ICP, in IOP, and in cerebral edema, the mannitol therapy protocol was designed as follows: Mannitol therapy with 500-mL mannitol 20% was started once daily or twice daily (equal to 100-200 g mannitol per day, based on the severity of the patient’s symptoms). The dose of mannitol was adjusted between 1-1.5 g/kg/dose according to clinical signs and their severity (ICP: 0.25-1 g/kg/dose, and IOP: 0.25-2 g/kg/dose [20]).

2. Each 500-mL mannitol 20% was infused with 500-mL D5NS solution through a Y-site over 4 hours to achieve the desirable initial 1000-mL doseroutine abdominal examination, pulmonary auscultation, abdominal circumference measurement, and evaluation of diuresis and hemoconcentration were performed for decision making on the continuation of fluid therapy and, if indicated, after 4 hours of infusion, 500-mL D5NS was infused over 30-60 minutes. The second infusion was not performed if examinations indicated progressive fluid retention in the body [21].

3. During the infusion, attention was paid to maintaining an adequate level of urine output (≥20-30 mL/h); mannitol therapy was continued until abdominal and pulmonary signs were completely resolved. One of the improvement indices in the management of OHSS is that the total fluid output exceeds the total fluid intake, which indicates termination of fluid retention. This trend (output>intake) should be carefully monitored and recorded to make sure that the complications of OHSS are controlled. If in a 24-hour period the total fluid output was not more than the total fluid intake, the patient was placed on NPO (nil per os, or nothing by mouth), and mannitol was administered twice daily along with 500 mL of D5NS solution followed by an infusion of 1000 mL of solution after each dose of mannitol. The type of solution was selected based on the clinical considerations explained in clinical notes 1 and 2, which follow. Once the output was greater than the intake, NPO was discontinued and the patient received mannitol as before on a daily basis.

Clinical note 1: In patients with diabetes, normal saline (0.9% saline) was used instead of D5NS.

Clinical note 2: According to the patient’s serum sodium (Na) level, dextrose 5% or half saline was used instead of D5NS to correct hyponatremia.

RESULTS

Of the 5227 women who entered the ovarian stimulation protocol for IVF over a period of 8 years from 2008 to 2016, there were 1205 OHSS cases (23.05%). Of these cases, 918 patients with mild OHSS comprised 76.18% of the total cases of OHSS and 17.56% of all induction cases. Moreover, 254 patients (21.08% of the OHSS cases and 4.86% of all the induction cases) had moderate and severe OHSS, respectively. Among patients with severe OHSS, types A, B, and C were observed in 28 (2.32% of the OHSS cases), four (0.33% of the OHSS cases), and one (0.083% of the OHSS cases) patients, respectively. In total, 287 patients (moderate and severe cases, or 23.8% of all the OHSS cases) were clinically important and received medical intervention (Table 1).

The pregnancy rate (based on positive β-hCG) among patients with different severities of OHSS was 13.1% (158 patients). No significant relationship was observed between the occurrence of pregnancy and the severity of OHSS (x² = 3.025, df = 2, P value = 0.224), as pregnancy was observed in 14.05% (129 patients), 10.24% (26 patients), and 9.09% (3 patients) of those women with mild, moderate, and severe OHSS, respectively. There was no significant correlation between body mass index (BMI) and the severity of OHSS (ANOVA F = 0.915, df = 2, P value = 0.522). The clinical pregnancy rate (based on gestational sac detection), was 12.6% in OHSS patients (13.5%, 9.4%, and 9.1% for mild, moderate, and severe OHSS, respectively). There was no significant correlation between the number of previous births and the severity of OHSS (ANOVA F = 0.224), as pregnancy was observed in 14.05% (129 patients), 10.24% (26 patients), and 9.09% (3 patients) of those women with mild, moderate, and severe OHSS, respectively (Table 2).

Approximately 66.7% of the patients with severe OHSS had a primary diagnosis of various types of polycystic ovarian disease (PCOD) that was significantly correlated with the severity of OHSS (x² = 17.42, df = 2, P value = 0.0002), as 37.8% and 32.8% of the patients with moderate and mild OHSS had a primary diagnosis of PCOD, respectively. The same was true for the history of PCOD because 48.5%, 29.9%, and 21.35% of the patients with severe, moderate, and mild OHSS had a previous diagnosis of PCOD, respectively (x² = 19.31, df = 2, P value <0.0001). Of all the patients with OHSS, 284 (23.6%) had a previous diagnosis of PCOD (Table 2).

Among the cases of secondary infertility, we found no significant relationship between the number of previous
Central

Saremi et al. (2017)
Email: saremias@yahoo.com

Primary pilot during the Iraq-Iran war and obtaining approval from the ethics committee of the medical center
- 5227 patients (the total number of patients who entered the study from April 2008 to February 2016)

1285 patients (23.09%): total number of OHSS cases in all of the patients

- Mild OHSS
  - 918 patients, 76.18% (17.56% of all of the patients who entered the protocol)
- Moderate OHSS
  - 254 patients, 21.08% (4.86% of all of the patients who entered the protocol)
- Severe OHSS
  - 33 patients, 2.74% (0.63% of all of the patients who entered the treatment protocol)

Type A: 28 patients, 2.32% of the cases of OHSS
Type B: 4 patients, 0.33% of the cases of OHSS
Type C: 1 patient, 0.083% of the cases of OHSS

Table 1: The frequency of the study patients and the results of treatment using the mannitol protocol.

**Table 2:** Pregnancy rates and history of PCOD in OHSS groups.

<table>
<thead>
<tr>
<th>OHSS Group</th>
<th>Number of Patients</th>
<th>Chemical Pregnancy Rate (Freq.)</th>
<th>Clinical Pregnancy Rate</th>
<th>History of PCOD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>918</td>
<td>14.05 (129)</td>
<td>13.5</td>
<td>48.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>254</td>
<td>10.24 (26)</td>
<td>9.4</td>
<td>29.9</td>
</tr>
<tr>
<td>Severe</td>
<td>33</td>
<td>9.09 (3)</td>
<td>9.1</td>
<td>21.35</td>
</tr>
<tr>
<td>Total</td>
<td>1205</td>
<td>13.1 (58)</td>
<td>12.6</td>
<td>-</td>
</tr>
</tbody>
</table>

Pregnancies or deliveries and the severity of OHSS (P<0.05).

In this study, the analyses of the outcome of treatment with Mannitol were performed on cases with moderate and severe OHSS. The mean age of these patients was 29.66 ± 4.27 years. Embryo transfer was cancelled in 260 patients (90.6%) with moderate and severe OHSS (4.97% of all OHSS cases). The mean number of follicles that are ≥14 mm in diameter in patients with moderate and severe OHSS was 16.65 ± 5.46. The mean number of transferred embryos in patients with moderate and severe OHSS, in whose embryo transfers were not cancelled, was 2.57 ± 0.53 (Table 3).

After mannitol therapy, the following results were obtained on comparing patients with moderate and severe OHSS before and after treatment. The mean weight loss after mannitol therapy

**Table 3: Clinical Outcomes for Moderate and Severe OHSS under Mannitol therapy.**

<table>
<thead>
<tr>
<th>Clinical Outcomes for Moderate and Severe OHSS</th>
<th>Percentage (Freq.) Or Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo Transfer Cancellation</td>
<td>90.6 (260)</td>
</tr>
<tr>
<td>No. of Follicle ≥14 mm</td>
<td>16.65 (5.46)</td>
</tr>
<tr>
<td>No. of Transferred Embryo</td>
<td>2.57 (0.53)</td>
</tr>
<tr>
<td>Mean Weight Loss (Kg) *</td>
<td>3.21 (6.22)</td>
</tr>
<tr>
<td>Mean D-Dimer level</td>
<td>0.51 (0.438)</td>
</tr>
<tr>
<td>Mean Osmolar Gap (mOsmol/kg)</td>
<td>13.76 (11.1)</td>
</tr>
</tbody>
</table>

*P-value<0.05
it should be noted that 12 and 7 patients with severe OHSS had a patient hospitalization period of 4.72 ± 2.92 days (range: 2-11 d).

Among all 287 patients, 27.9% had oliguria (<0.5 mL/kg/h), (4.2% had severe oliguria, <0.1 mL/kg/h), and the remaining patients had an adequate urinary output. After treatment, the rate was reduced to 17.4% for oliguria (1.4% had severe oliguria), which was significantly different (P<0.05). The mean 24-hour urinary intake/output difference was -349.60 ± 1289.81 mL in the patients before treatment, and increased to 641.80 ± 1032.54 mL after treatment, indicating a significant difference (paired t-test, t = -2.843, df = 285, P-value = 0.0048). Correction of the hemoconcentration was observed after mannitol therapy, but it was not statistically significant (P=0.05) (Table 4).

No mortality occurred in patients on Mannitol therapy during the study period. Two patients developed severe complications due to OHSS, because of the failure in their care to follow the mannitol therapy protocol. The first case was a 36-year-old woman with primary infertility. The signs of moderate-to-severe OHSS were observed after ovarian stimulation in this patient, and she had inadequate urinary output. The protocol was not observed in this patient, and the patient received more than the maximum dose of mannitol (5000 mg/kg/day). She also received 1400 g mannitol for 7 days, which should not have exceeded 100 g. This patient was hemodialyzed once and recovered after 3 days of hospitalization. Pregnancy did not occur in this patient. The second case was a 24-year-old woman with primary infertility who was placed on mannitol therapy despite oliguria and received approximately 1300 g of mannitol in 8 days (13 doses), which was again more than the maximum allowable dose defined in our protocol.

Another major outcome of the mannitol therapy was a mean patient hospitalization period of 4.72 ± 2.92 days (range: 2-11 d). It should be noted that 12 and 7 patients with severe OHSS had abdominal discomfort and respiratory distress before treatment, respectively, which resolved with mannitol therapy.

**DISCUSSION**

Although the precise pathophysiologic pathways of OHSS are unclear, some seem to be more important. Increased vascular permeability is caused by vasoactive substances that are produced by hyperstimulated ovaries, with vascular endothelial growth factor (VEGF) being the most important [2,3,5]. The role of VEGF in the pathogenesis of OHSS has been widely investigated by researchers [5,24-28]. According to in vitro studies, hCG is a strong stimulator of ovarian granulosa cells for the secretion of vascular endothelial growth factor (VEGF), which can explain the clinical relationship between hCG and OHSS [2,5]. VEGF plays a major role in increasing the capillary permeability in OHSS-related ascites [5,8]. In addition, the role of inflammation-related cytokines and interleukins [10,24], inhibit A and B, selectins (like E-selectin), the von Willebrand factor, immunoglobulin changes, metabolic changes [8], and the renin-angiotensin system in the development and severity of OHSS has been demonstrated [29,30]. It is not clear whether mannitol can interact or bind with any of these factors, especially VEGF, to manifest its efficacy besides its osmotic diuresis and volume expansion. More investigations are needed to understand these molecular mechanisms.

The molecular structure, mechanism of action, contraindications, precautions, and recommended dosage of mannitol administration were all considered in the protocol design for the management of OHSS. Mannitol is very hydrophilic due to the presence of numerous alcohol groups (-OH) in its molecular structure. The molecules of water bind to each mannitol molecule through hydrogen bonds and cause its osmotic-diuretic properties.

In our study, the incidence of mild, moderate, and severe OHSS in patients was slightly less than those previously reported [1,2]. Weight gain, discomfort, and respiratory distress, as the indices of OHSS, improved significantly after treatment. The correction of oliguria or anuria and the urine intake/output trends were significant after treatment. The diuretic effect of mannitol and adequate diuresis indicate achievement of the treatment objectives. Concerning the fact that there was no significant correction of the hemoconcentration, it should be noted that in a constant volume of red blood cells, the change in hematocrit is never numerically commensurate with the change in plasma volume, and the change in the plasma volume is of greater clinical relevance than the change reflected by hematocrit. In other words, an increase of 2 units in hematocrit from 45% to 47% is four times less than the actual 8% decrease in plasma volume and the severity of the disease. Similarly, even small decreases in hematocrit level during treatment may indicate significant improvements in plasma volume and the overall condition of the patient [8]. It is very important to pay attention to this issue during patient monitoring.

The mean D-dimer level was within the normal range in all of our patients. The mean and maximum osmolality and the mean and maximum osmolar gap during mannitol therapy confirmed the safety of the dose of mannitol in the designed protocol and indicated no mannitol accumulation in the intravascular space.

The mean duration of hospitalization in our study population was significantly shorter than previously reported in albumin therapy. A considerable decrease in costs as a result of the decrease in inpatient bed occupancy and the much lower cost of mannitol compared to albumin or hydroxyethyl starch was
another advantage of this protocol in the management of OHSS. In additionally, not canceling IVF cycles prevents abortive costs. Considering the high number of patients with moderate-to-severe OHSS in our study (377 patients), the lack of mortality and only two cases of morbidity were additional favorable results of this protocol.

There were some changes that are necessary for better and more reliable results for our recent study. Compare to our previous experiment, the difference of the current study are; Usage of the unique induction protocol especially for the high-risk (e.g. PCOS) patients (so more reliable statistics for OHSS prevalence were given and for all patients in the view of the induction method), D-Dimer check in the patients (whereas We had not used the Heparin in our patients routinely, because of the low level of D-Dimer) and Non-use of Paracentesis in patients (So, the risk of infections was reduced and loss of albumin was not occurs) [31]. It must be mentioned that, the lack of the control group in this study is the major limitation of the study that can be followed by a RCT study for confirmation of the Mannitol therapy efficacy.

CONCLUSION

The results of our study showed the benefits of mannitol in the management of OHSS. According to our findings, the effects of mannitol therapy on controlling the signs and symptoms of OHSS, the major indices of patient improvement, and the mortality and morbidity rates are acceptable. In additional, mannitol therapy is tremendously effective at saving money for the health system. Finally, we suggest further randomized controlled studies to compare the efficacy of mannitol with other available methods and medications in the management of OHSS. For this reason a RCT study is undertaken by our research group in this field.

ACKNOWLEDGMENTS

The authors wish to thank all colleagues at the supporting institutes: Sarem Women’s Hospital and Sarem Fertility and Infertility Research Center (SAFIR). Special thanks to Mrs. Leila Zand Azad, Mrs. NooshinFarahbakshkh, and Mrs. FaezehMoalemGhamsari for helping us gather data.

REFERENCES

Seminars in reproductive medicine. 2010; 28: 532-539.


