Calcium infusion for the prevention of ovarian hyperstimulation syndrome: a double-blind randomized controlled trial

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Objective: To evaluate the role of calcium infusion as a preventive strategy of ovarian hyperstimulation syndrome (OHSS) in women at high risk in in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment cycles.
Design: Double-blinded randomized controlled trial.
Setting: University hospital department of obstetrics and gynecology and private IVF center.
Patient(s): Two hundred women at risk to develop OHSS undergoing IVF/ICSI treatment cycle.
Intervention(s): The intervention group (group 1; n = 100) received intravenous infusion of 10 mL 10% calcium gluconate in 100 mL 0.9% saline solution on the day of ovum pick-up (OPU) and days 1, 2, and 3 after, and the placebo group (group 2; n = 100) received 100 mL 0.9% saline solution on the day of OPU and days 1, 2, and 3 after.
Main Outcome Measure(s): Incidence of OHSS.
Result(s): OHSS incidence was significantly higher in the placebo group (group 2) than in the calcium infusion group (group 1): 23 (23%) vs. 7 (7%); moderate OHSS was significantly higher in group 2 than in group 1: 8 (8%) vs. 1 (1%); and severe OHSS was significantly higher in group 2 than in group 1: 4 (4%) vs. 0.
Conclusion(s): Intravenous calcium infusion effectively reduced the incidence of OHSS development without reduction in the pregnancy rate.
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Key Words: OHSS, calcium infusion, RCT, PCO

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The most potentially severe complication of controlled ovarian hyperstimulation is ovarian hyperstimulation syndrome (OHSS) (1). OHSS is considered to be a serious complication with high probability of morbidity and mortality (2). It consists of a variety of symptoms and signs that include increased vascular permeability with subsequent third space fluid collection, ascites, abdominal discomfort, and abdominal distension and enlarged ovaries (3). OHSS could present as one of two forms (early or late); the form that presents within 9 days after hCG administration is the early-onset form, and the form that presents after hCG injection by $\geq$10 days is called the late-onset form because of hCG released by the trophoblast (4). Several treatment modalities have been used to decrease the incidence of moderate and severe OHSS, namely coasting (5), cycle cancellation (6), cryopreservation of embryos (7), cabergoline (8), intravenous (IV) fluids, such as albumin (9), replacing FSH with low-dose hCG (10), the use of the antagonist protocol instead of the agonist protocol (11), and replacing hCG with a GnRH agonist to induce final follicular maturation (12).

The pathophysiology of OHSS is characterized by increased capillary permeability, leading to leakage of fluid into the third space from the vascular compartment, with third space fluid accumulation (3). Vascular endothelial growth factor (VEGF) has emerged as one of the factors most likely involved in the pathophysiology of OHSS (13).

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Plasma renin level and renin activity have been shown to be increased in OHSS (14). Angiotensin II levels were 100 times higher in OHSS ascites fluid compared with non-OHSS ascites fluid (15). Angiotensin II was found to increase VEGF secretion locally (16).

In a recent retrospective study it was hypothesized that calcium infusion can inhibit the renin-angiotensin system (RAS) and consequently decrease the VEGF level with a reduction in OHSS incidence (17). Gurgan et al. found that calcium infusion could successfully prevent the development of severe OHSS and significantly decrease OHSS occurrence rates without any major adverse effect when used for high-risk patients (17).

To our knowledge, there are no randomized trials to date that have studied the protective effect of IV calcium infusion from OHSS in high responders undergoing an in vitro fertilization (IVF) cycle. The aim of the present study was to study the incidence of OHSS and clinical outcomes after calcium IV infusion on protocol for IVF/intracytoplasmic sperm injection (ICSI) in patients at very high risk for the development of OHSS.

MATERIALS AND METHODS

This was a double-blind randomized prospective controlled study involving patients undergoing ICSI cycles at two IVF centers (Kasr Al-Aini IVF Center, Faculty of Medicine, Cairo University, Cairo, Egypt; and Middle East IVF Center, Giza, Egypt). Institutional Review Board approval was obtained for the study. All couples with risk for developing OHSS received written and verbal information about the study and were asked to participate. Those who agreed signed an informed consent form.

We enrolled patients undergoing ICSI from October 2011 to September 2013 who were at risk of developing OHSS. The risk of developing OHSS was defined as follows: E_2 level on day of hCG >2,500 pg/mL with at least 20 follicles ≥10 mm on the day of hCG administration based on earlier clinical observation. Patients with E_2 ≥6,000 pg/mL were excluded from the study as decided by the Research Ethical Committee, because they found that it is not ethical to give just placebo to patients with E_2 level >6,000 pg/mL in the control placebo arm with a high possibility of severe OHSS.

Sample size was calculated to prevent type II error. Earlier data indicated that the OHSS rate among control subjects was 16.2% although the OHSS rate with calcium infusion 3.6% (17). Based on these data, we would need to study 87 cases in each arm to be able to reject with a probability of 80% the null hypothesis that the rates for the experimental and control groups are equal. The type I error probability associated with this test for the null hypothesis was 0.05. We used an uncorrected chi-square statistic to evaluate this null hypothesis. Additionally, to compensate for subjects declining to participate or lost to follow-up, we recruited 110 women for each arm. Five cases in the intervention group and six cases in the control group had earlier failed IFV cycles, of which one case of moderate OHSS in each group was diagnosed.

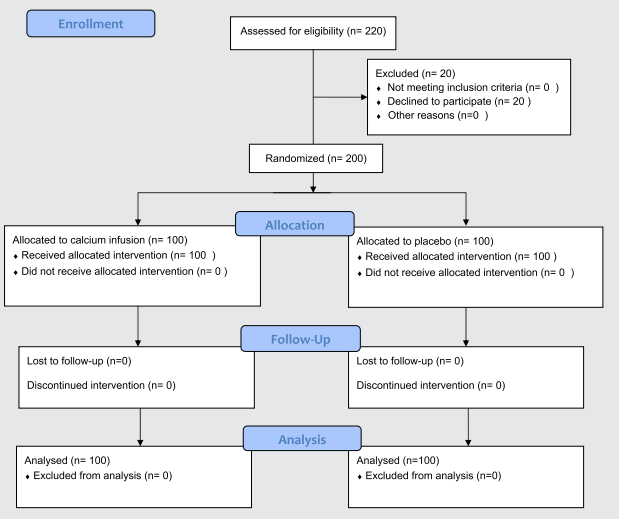
All patients were preoperatively evaluated by a cardiologist for possible toxic effect of IV calcium infusion, in the form of history taking and electrocardiography to exclude arrhythmia and to exclude digitalis intake, because the injection of calcium preparations is strictly contraindicated in digitalis patients because it may precipitate (or exacerbate) digoxin-induced cardiotoxicity.

Two-hundred twenty eligible patients at risk for OHSS were randomly allocated to either the intervention group (group 1) or the placebo group (group 2; Fig. 1) with the use of computer-generated random number tables and opaque sealed envelopes containing the participants' group allocation. The envelopes were prepared every 24 hours at a location different from the study site and sent to an assigned nurse, who opened each envelope just before ovum pick-up (OPU). The patients and the staff who followed up the patients were blinded to the allocation to avoid bias.

In the calcium infusion group (group 1), 10 mL IV 10% calcium gluconate in 200 mL physiologic saline solution on the day of ovum pickup and days 1, 2, and 3 after ovum pick-up was administered within 30 minutes, as previously described by Gurgan et al. and Yakovenko et al. (17, 18). In the placebo group (group 2), IV 200 mL physiologic saline solution on the day of ovum pick-up and days 1, 2, and 3 after ovum pick-up was administered within 30 minutes.

All of the patients included were undergoing ICSI cycles through the long protocol, in which the patients start the cycle of treatment with the use of oral contraceptive pills on day 4 preceding the cycle, down-regulation starts in the midluteal phase on day 20 of the cycle with the use of daily subcutaneous injections of GNRH agonist triptorelin (0.1 mg Decapeptyl; Ferring). Ovarian stimulation started after the patient was down-regulated (as evidenced by endometrial thickness <5 mm and/or E_2 levels <50 pg/mL) on day 2 or 3 of her

FIGURE 1



Flow chart.

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