Effect of nifedipine administration before embryo transfer on reproductive outcome in ICSI cycles, a double-blind control trial study

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Abstract

Purpose: Nifedipine is a calcium channel blocker with smooth muscle relaxing properties. This study set out to investigate the efficacy of nifedipine administered orally before embryo transfer (ET) on the improvement of the Intracytoplasmic sperm injection (ICSI) outcome.

This double-blind placebo-control trial study was carried out in Babol (Iran) in 2019- 2020. 200 infertile women undergoing ET treatments were randomly allocated to receive nifedipine 20 mg tablets placebo orally 30 minutes before ET. The primary outcome was the chemical pregnancy rate. Implantation rate and clinical pregnancy were considered as the secondary outcome.

Result: There is no significant difference (P> 0.05) in the number of oocytes and quality of embryos in the nifedipine and placebo groups. Despite increases in the rate of a chemical pregnancy, there were no statistical differences in the study group versus the comparison group (24% vs 14%, P=0.1, rate ratio 0.88, 95% CI, 0.77 to 1.01) respectively. In implantation rate, no statistically significant difference between the two groups was evident (20% vs 10%, P=0.07, rate ratio 0.88, 95% CI, 0.79 to 1.00) respectively. Also, no significant increase in clinical pregnancy was found compared with the placebo (17% vs 8%, P=0.26, rate ratio 0.90, 0.81 to 1.00).

Conclusion: Nifedipine administered orally 30 minutes before embryo transfer did not improve the chemical pregnancy rate, implantation rate, or clinical pregnancy rate in women undergoing ICSI.

Introduction

The implantation window in the assisted reproductive technology (ART) initiates from days 18 to 22 in ovarian stimulation cycles (Nikas & Aghajanova, 2002). The success of embryo implantation is multifactorial. The most important factors are uterine receptivity, female age, and embryo quality [1]. The uterine ability to accept the embryo and nourish it varies from woman to woman even if the other conditions are the same. In recent studies, the investigation showed some inflammatory-based defects interfere in the endometer receptivity in the women undergoing ART [2]. The scientists examined some anti-inflammatory interventions such as platelet-rich plasma (PRP), endometrial scratching, and acupuncture and concluded they may improve ART outcomes especially in women with repeated implantation failure through secreting of cytokines, interleukins, and growth hormone and healing the damaged endometrium [3–6].

Besides, anti-inflammatory medicines such as aspirin or heparin were studied to improve increasing blood flow and preventing vascular thrombosis at the embryo implantation site [7, 8]. Investigators guess that other medications such as calcium channel blockers (CCB) that are non-specific smooth muscle relaxants with the mechanism of reducing peripheral and cerebral vasospasm that may have a similar impact on the endometer. Nifedipine is a CCB that has been an efficient tocolytic agent for the management of the preterm labor frequently used as a tocolytic in premature labor [9, 10], however much less is known about the use of that on the ART outcome. Except for one similar study on ART outcome

conducted by Ng et al, there is no controlled study comparing the difference between a group receiving nifedipine and the placebo. In their study 20mg nifedipine were given 30 minutes orally before embryo, however, the implantation rate or the clinical pregnancy rate did not show any statistical differences [11]. Despite the good design of the study, their research was limited to 46 women in the nifedipine group, compared with 47 women in the placebo [11]. This trial study with greater samples set out to assess the effect of nifedipine before the embryo transfer on the ICSI outcome.

Materials And Methods

The research ethics committee of Babol University of Medical Sciences approved this study (Reference number: IR.mubabol.HRI.REC1397.209). This interventional double-blinded randomized placebo controlled trial was registered with number IRCT20180417039338N3 in the Iran registry of clinical trials (IRCT). The trial was done in Babol Infertility Center from April 2019 to May 2020.

Eligibility criteria include women candidate for frozen embryo transfer, 18–40 year, BMI < 35 and FSH < 14mli/IU in early follicular phase (day 2–3), premature ovarian failure and uterine cavity complication recorded, no history of heart or liver diseases, baseline blood pressure (BP) equal to 100/60 (mmHg) or more measured before embryo transfer, patients being treated with hypotension medications, and who had not contraindication for taking nifedipine.

Those with BP equal to 100/60 (mmHg) or less for any reasons half hour before embryo transfer, patients who decline to participate the study and the ones taking medications interacting with nifedipine excluded. Before randomization, the trial protocol was fully described to the participants and informed consent was taken. Since the pregnancy rate was showed no difference using various methods of endometrial preparation pre-embryo transfer, both routine preparation protocols (the natural cycle protocol or artificial protocol) were accepted and applied [12].

Randomization and Intervention

Sample size was calculated according to a significance level of 0.05 and, a power level of 0.80. The minimum sample size was determined 100 women in each group and the allocation ratio into each arm was 1:1. All blocking and random allocation were performed by the University's statistics center. The statistician used an online randomization site for random block assignment. They produced a permuted block-sized numbers with block-8 and offered that to a trained nurse. The list was concealed of the principal researchers. The nurse as a third person that was not involved the study, allocated the participants to the group A or B according to the blocked numbers on the day of embryo transfer and cleaned the list immediately after the allocation.

The medicines contain 100 tablets of nifedipine 20 mg (Tolidaru co., Iran) and 100 tablets placebo that were given orally. The researcher inserted each tablet into a small uni-shape capsule and packed in the uni- shape pocket and coded A or B. 30 minutes before ET, participants' blood pressure were taken with a digital arm BP measuring device (Microlife, Widnau, Switzerland)) and if it was 100/60 (mmHg) or more,

the mentioned nurse administered the pockets A or B to the patients according to the blocked numbers. BP and possible adverse events were checked 30 minutes post-ET. The participants, the sonographer of endometer monitoring, the embryo transfer physician, and staff of the ICSI laboratory were not aware of the allocation. The nurse also recorded the details of the demographic characteristics, oocyte and embryo quality (after warming) and pregnancy outcomes of the patients according to their codes. Embryo quality was defined using a scoring system based on the cell number and regularity of blastomeres as well as the rate of fragmentation. Good quality embryo (A and B) was including stage-specific cell size, no multinucleation, and maximum 10% fragmentation according to Eshre consensus guidline 2011 [13]. Then outcome assessor inserted the recorded data to the checklist and then to the SPSS software and analyzed.

Outcome assessment

The primary outcome was chemical pregnancy rate that was defined as serum human chorionic gonadotropic > 190 IU/L in the frozen embryo recipients) 16 days following embryo transfer were in the nifedipine group and the controls [14]. Implantation rate was considered as the secondary outcome and defined as visualization of the gestational sac in the vaginal ultrasound image in 5–6 weeks following chemical pregnancy confirmed [15]. Another secondary outcome was the clinical pregnancy that defined as ultrasound confirmation of fetus heartbeat after 6–8 weeks following chemical pregnancy confirmed [16].

Outcome analysis

Statistical tests were done using SPSS 16 (SPSS Inc., Version 18, Chicago, IL, USA). Kolmogorov-Smirnov tests applied to assess the normality of quantitative variables. Data were presented as mean and standard deviations (mean ± SD). A 2-tailed p-value of 0.05 or less was considered statistically significant. Intention-to-treat principle (ITT) was applied in the analysis.

T-test determined the mean difference of parameters between the study groups and the control.

Results

After applying restrictive eligibility on the patient who candidate frozen embryo transfer, 220 women were selected. 19 women were excluded; 16 women met no inclusion criteria, two women had the exclusion criteria (one woman for receiving nifedipine during the week before embryo transfer, one woman for the blood pressure less than 100/60 (mmHg) half-hour pre-embryo transfer, and two women declined to participate. 200 patients were entered and allocated to two groups (100 women in the nifedipine group and 100 women in the placebo group). All women in the intervention group and 99 women in the comparison group continued the intervention to the end of the study. The woman who lost the follow up in the placebo group did not excluded the analysis. (Flowchart1).

Table 1 summarized the demographic criteria, oocytes and embryos quality in the study and comparison groups. Baseline characteristic was showed no significant differences in both groups. As a whole, 47.2% of the transferred embryos in the intervention group and 52.8% in the comparison group were in the quality A. The transferred embryos in quality B were 46.9% in the nifedipine group and 53.1% in the placebo group. There was no significant difference ($P > 0.05$) in the number of oocytes and quality of embryos in the nifedipine and placebo groups.

Table 1
Baseline characteristic of the ICSI patients participated in the study

		Nifedipine group (n = 100)	Comparison group (n = 100)
Age		32.55 ± 4.87	31.52 ± 4.34
BMI		26.45 ± 3.52	26.5 ± 3.6
Infertility duration		5.96 ± 3.89	6.29 ± 4.29
Gravidity	0	79%(79)	75%(75)
	1	13%(13)	20%(20)
	≥ 2	8%(8)	5%(5)
Previous ART	0	81%(81)	81%(81)
	1	14%(14)	13%(13)
	≥ 2	5%(5)	6%(6)
Cause of infertility	Tubal	21%(21)	17%(17)
	Uterine	6%(6)	5%(5)
	Male	53%(53)	59%(59)
	Both	11%(11)	7%(7)
	Unexplained	23%(23)	23%(23)
FSH		6.44 ± 3.54	6.01 ± 2.95
LH		6.19 ± 4.56	5.71 ± 3.67
Number of oocyte retrieved		9.02 ± 6.26	10.49 ± 6.78
Number of frozen embryo transferred		5.43 ± 3.92	6.16 ± 3.97
Quality of embryo transferred	Good	3.62 ± 2.71	3.70 ± 2.74
	Medium	2.39 ± 1.69	2.74 ± 2.07
	Weak	2.18 ± 1.59	1.73 ± 0.99
The values were shown as Mean ± SD and percentage.			

Table 2 presents the pregnancy outcomes in the nifedipine group versus placebo. Despite with successive increases rate of chemical pregnancy as the primary outcome, there was no statistical differences in the study group versus the comparison group (24% vs 14%, P = 0.1, rate ratio 0.88, 95% CI, 0.77 to 1.01) respectively. In the implantation rate, no statistically significant difference between the two groups was

evident (20% vs 10%, P = 0.07, rate ratio 0.88, 95% CI, 0.79 to 1.00) respectively (Table 2). Also, no significant increase in clinical pregnancy was found compared with placebo (17% vs 8%, P = 0.26, rate ratio 0.90, 0.81 to 1.00). One patient in the nifedipine group and one patient in the placebo group had ectopic pregnancy (Table 2).

Table 2
Comparison of teproductive outcome of the women received intervention

	Nifedipine group(n = 100)	Placebo group(n = 100)	P-value	Rate ratio (95% confidence interval)
Chemical pregnancy	24/100 (24%)	14/100 (14%)	0.1	0.88 (0.77 to 1.01)
Implantation rate	20/100 (20%)	10/100 (10%)	0.07	0.88 (0.79 to 1.00)
Clinical pregnancy	17/100 (17%)	8/100 (8%)	0.26	0.90 (0.81 to 1.00)
Ongoing pregnancy	14/100 (14%)	8/100 (8%)	0.25	0.93(0.84 to 1.03)
Ectopic pregnancy	1/100 (1%)	1/100 (1%)	1.0	1.00 (0.06 to 15.77)
Misscariage	6/100 (6%)	4/100 (4%)	0.75	1.5(0.44 to 5.15)
Pearson chi-square test				

Hypotension was not seen in any participants 30 minute following embryo transfer.

Discussion

In the present study, nifedipine before embryo transfer did not improve the chemical pregnancy rate and implantation rate and also the clinical pregnancy. These results reflect those of Ng et al., who also found no evidence that the group that received nifedipine 30 minutes before embryo transfer showed a greater clinical pregnancy rate versus the comparison group who did not receive placebo (RR 1.155, 95% CI (0.450–2.966)). Ng et al considered 46 women candidates for embryo transfer who were received nifedipine compared with 47 women who were given the placebo [11]. The insufficient sample size was one of the limitations that they mentioned in their paper. We recruited 200 women candidates for embryo transfer and divided them into two groups in the 1: 1 ratio. The sample size in our study was sufficient, however, the rate of implantation and clinical pregnancy in our study did not improve similarly to their findings. It is noteworthy that implantation rate was the secondary outcome in our study and the primary outcome in Ng's study. Also, the pregnancy rate that Ng et al reported was greater than our result [11]. Many factors such as the quality of embryo and the receptivity of the endometrium are effective in pregnancy. Though we only transferred good quality embryos, however we required to consider patients'

preferences and medical advices in the endometrial preparation. This discrepancy may partly be explained by that. Also at the present study, the rather contradictory result may have been perticularly influenced by the women with the polycystic ovary and endometriosis and who with a history of repeated implantation failure that we did not exclude them from the study. Undoubtfully, this is a limitation of our study.

Except for Ng's study, very little was found in the literature on the question of the efficacy of calcium channel blockers on the outcome of patients undergoing IVF. It limited the comparison of the present study with similar studies to us. It is unfortunate that the study did not initiate with the higher dose of nifedipine and also its doses were not repeated, because the investigators were unsure about its vaginal side effects, uterine receptivity, and potential teratogenic effects on embryos. In an animal study, Banerjee previously found that calcium diltiazem as a channel blocker drug may significantly reduce implantation when it was injected into the uterine of mice 12–14 h before implantation [17]. He concluded that the use of the calcium channel blocker failed uterine receptivity through other independent mechanisms without interfering with estrogen-progesterone control. More broadly, research is needed to determine whether a further dose of this medicine can improve fertility after safety is guaranteed.

Conclusion

This study confirmed that nifedipine administered orally 30 minutes before embryo transfer did not improve the chemical pregnancy rate, implantation rate, or clinical pregnancy rate in women undergoing ICSI.

Declarations

Conflict of interest

None

Author Contribution

FA Basirat: Project development, Data Collection, Data analysis

ZA Basirat: Manuscript writing/ editing, Project development

SE Esmaeilzadeh: Project development, Data Collection

FA Ghofrani: Data Collection

MA Golsorkhtabar: Manuscript writing, Data analysis

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Figures

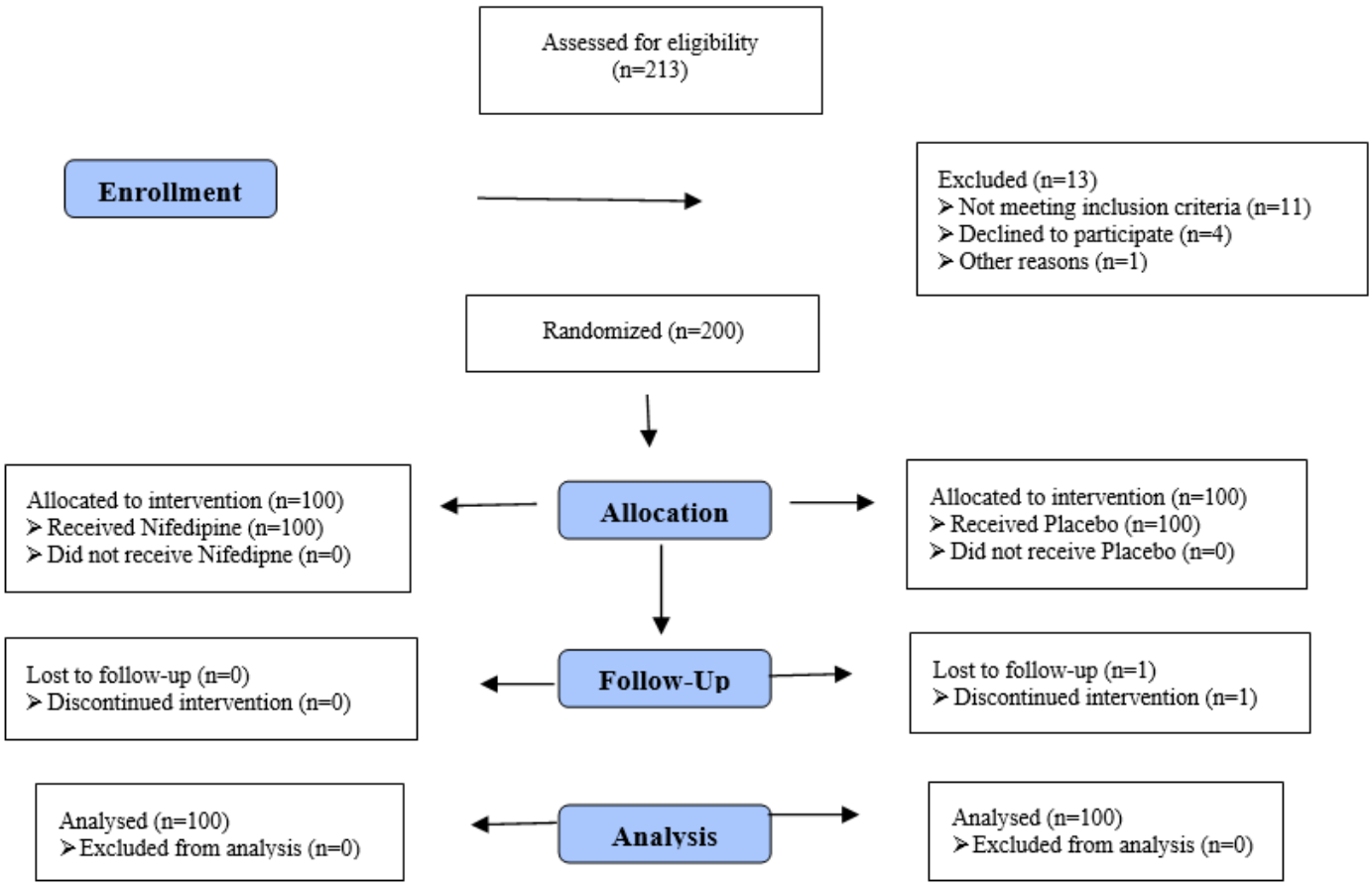

Figure 1

Treatment flow of participants in the intervention and comparison groups