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Could Artificial Oocyte Electro -Activation Timing Affect the Fertilization Rate in Post-Intracytoplasmic Sperm Injection (ICSI)?

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Abstract

Background: Intracytoplasmic Sperm Injection (ICSI) related fertilization failure has been of utmost importance in research since the technique was discovered. The search for the root cause, including that of male factor infertility, has been investigated heavily in the past decade. One of the efforts made to solve this issue was the introduction of artificial oocyte activation (AOA) which was designed to combat this unfortunate outcome.

Aim of Study: To review the electroactivation technique for artificial oocyte activation and the impact of its different timing on ICSI in severe male factor cases.

Study Design: This study is a prospective randomized control study.

Setting: The Egyptian IVF-ET center (a private IVF center in Egypt) in cooperation with the Genetic Engineering and Biotechnology Research Institute, University of Sadat City.

Patients: Seventy-six participants were chosen for the study, all of them had either severe oligoteratoasthenospermia, non-obstructive azoospermia with complete teratospermia, or fully immotile spermatozoa. Patients who had total or limited fertilization post ICSI procedure were also included.

Intervention: After the pick-up procedure, the collected oocytes (n=862) from 76 patients were randomly divided after ICSI into two groups: The study group A (n=408) was subjected to electroactivation, and the control group B (n=454) with no electroactivation. The cases included in the study group were divided into two groups: Group (I) includes cases that were electroactivated within 30 minutes after ICSI (n=34) while group (II) included cases that were electroactivated in 2 hours after ICSI (n=42).

Main Outcome Measures: Fertilization and degeneration rate.

Results: Seventy-six ICSI cycles were included in the study. Electro activated group had a considerably greater fertilization rate than the control group (63% vs. 41%). The oocyte degeneration rate was not statistically significant between the two groups (1% vs 0%). On the other hand, the fertilization rate was statistically significantly higher in group (II) as compared with group (I) (70% vs 52%). Non-significant difference was observed between the two groups regarding the oocyte degeneration rate (0.5% vs 0.4%). Although limited fertilization resulted in 17 cycles in the control group and 6 cycles in the study group, total fertilization failure (TFF) appeared in only 3 cycles and embryo transfer were cancelled.

Conclusion: Some selected patients with limited fertilization potential may benefit from artificial oocyte activation (AOA) employing an electroactivation approach. Performing electroactivation in 2 hours after ICSI resulted in a significantly higher fertilization rate compared to direct or within 30 minutes electroactivated cases, such result if applied may lead to a better fertilization outcome in lab practice.

Key Words: *Artificial oocyte activation – Electrical activation – Failed fertilization – Fertilization rate – ICSI.*

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Introduction

THE work on human reproduction has always faced both scientific and ethical problems, which initially delayed the advancement of infertility treatments. However, our understanding of the events in human fertilization grew to the point along with innovation of assisted reproductive technologies (ART) which introduced many advances approved by the medical society to overcome the difficulties that caused infertility.

Intracytoplasmic Sperm Injection (ICSI) is increasingly being used in populations for whom conventional in-vitro fertilization (IVF) may be an option due to its higher fertilization rates of up to 65-80% [1], especially in cases of non-male

factors infertility, ranging from 69% in Europe to 100% in the Middle East, South-East Asia, and South America [2].

Fertilization is a multi-stage process that takes 24 hours to complete. When a male sperm fertilizes a female ovum, a zygote is formed, marking the beginning of a pregnancy that will last for around 280 days [3].

Five percent to ten percent of conventional IVF cycles end in total fertilization failure (TFF). TFF is defined as the failure of fertilization in all oocytes. Even with ICSI, human oocytes fail to fertilize around 30% of the time, where TFF happens in 2-3% of ICSI cycles. Contrary to ICSI, where oocyte activation problems are the most common cause of fertilization failure, sperm abnormalities are the most common cause of conventional IVF failure. If a couple has a fertilization failure, there is a 30% chance that it will happen again in consecutive cycles, demonstrating that it is not completely random and may be predicted and treated [4].

The emergence of such fertilization difficulties after ICSI prompts the inquiry into their root cause, in particular the function of the male gamete in the oocyte fertilization process. Total Fertilization failure during ICSI has been linked to oocyte defects, sperm abnormalities such as globozoospermia, teratozoospermia, and immotile spermatozoa [5], and even the ICSI process itself, according to a number of experimental investigations [6].

The sperm defects that may be responsible for failure in fertilization after ICSI procedure might be attributed to no or very low sperm viability, abnormal chromatin status, inability of the sperm nucleus to decondense, inability of sperm to activate oocytes [6].

As sperm release oocyte activation factor (SOAF) from their post-acrosomal sheath (PAS) or equatorial area, the oocyte becomes more permissive to fertilization. Although several variables have been speculated to play a role in SOAF activation, recent evidence suggests that phospholipase C zeta (PLCζ), an enzyme unique to sperm, is the primary SOAF activator. Hydrolysis of phosphatidylinositol 4, 5-bisphosphate (PIP2) by PLCζ results in the production of inositol-1,4,5-triphosphate (IP_3) and diacylglycerol (DAG) upon its release from sperm into the oocyte. IP_3 promotes calcium release from endoplasmic reticulum into the oocyte cytoplasm, where it triggers calcium oscillations that activate the oocyte and the resume of the meiotic process [7].

Male infertility has been linked to mutant forms of PLCζ, as shown by several studies, who also showed that PLCζ is expressed in the sperm PAS and plays an essential function during fertilization. In addition, sperm with abnormal morphology or sperm with a small or absent acrosome (globozoospermia) are unable to reach the zona pellucida and have a reduced capacity for activating the oocyte. As a result, oocytes may not be activated properly. This may be related to poor or no PLCζ expression. Many investigations shown a functional relationship between sperm PLCζ expression and the capacity to initiate calcium oscillations and activate oocytes [7].

In an effort to solve this issue, artificial oocyte activation (AOA) has been designed to combat unsuccessful fertilization during ICSI. Chemical stimulation [such as Ca^{2+} ionophores (e.g., ionomycin and calcimycin) and strontium chloride ($SrCl_2$)], mechanical stimulation, and electrical stimulation are often used in clinical practice for AOA, even though the procedure's effectiveness and safety have not been yet fully established. Patients with a history of complete fertilization failure or poor fertilization rates after ICSI have sparked growing interest in the use of ICSI in tandem with assisted oocyte activation (ICSI-AOA) [8].

The purpose of this study is to examine the timing of electroactivation procedures for artificial oocytes and their effect on the success of Intracytoplasmic Sperm Injection (ICSI) in cases of severe male factor.

Material and Methods

Patient selection:

Seventy-six individuals were chosen for this investigation due to their severe oligoteratoasthenospermia, complete teratospermia, nonobstructive azoospermia, or entirely immotile spermatozoa. Patients who had total fertilization failure or limited failure with ICSI were also considered. The included seventy six ICSI cycles were randomly divided into two groups: Group (I) included cases that were electroactivated within 30 minutes after ICSI (n=34) while group (II) included cases that were electroactivated in 2 hours after ICSI (n=42), the oocytes in each group (n=862) were randomly divided into a study group (A) that were subjected to electroactivation (n/I=198, n/II=188), and the control group (B) with no electroactivation (n/I=216, n/II=266).

Seventy-six patients undergoing ICSI who met the study's initial inclusion/exclusion criteria were

asked to participate and written consents were obtained with the initial gynecologist consultation.

Ovarian stimulation:

The long GnRH-agonist down-regulation protocol was used to induce ovulation in a controlled manner. Starting on cycle day 20, a GnRH agonist was administered (Decapeptyl, 0.1mg SC once daily; Ferring Pharmaceuticals, Copenhagen, Denmark). After E2 levels dropped to below 50pg/mL, confirming the down regulation, hMG was administered. This process typically takes 2-3 weeks. The first hMG dose ranged from 150 to 300mIU/d, depending on the patient's age, weight, and the responsiveness of the ovaries in prior cycles. Daily E2 measurements and vaginal ultrasonography began on day 7 of hMG stimulation. hCG (Pregnyl, 10,000 IU; NV Organon, the Netherlands) was administered when the mean diameter of three or more follicles reached 18 millimeters. The collection of oocytes was to take place 36 hours following the hCG injection.

Semen samples:

Patients with non-obstructive azoospermia who underwent testicular sperm extraction (TESE) provided tissue samples. Dissected testicular tissues were cultured in Ham's F-10 medium supplemented with 0.4% human serum albumin on a petri dish. Following a 5-minute spin in a centrifuge set at 1,460 rpm, the pellet was suspended in Ham's F-10 medium (Irvine scientific, USA) and subjected to another spin. The sample was then incubated at 37 degrees Celsius with 6% carbon dioxide with constant humidified conditions.

Laboratory procedures:

After oocyte retrieval, oocytes were incubated in culture media (Global Total LGGT, Life Global, USA) and treated in hyaluronidase (Irvine scientific, USA). Oocytes were washed in fresh Ham's F-10 media (Irvine scientific, USA) and transferred to LGGT under oil in a Falcon 1006 dish (Falcon, Franklin Lakes, NJ, USA) prepared for ICSI. In ICSI, individual oocytes were placed in droplets of buffered culture media (Global Total LGGT, Life Global). A drop of polyvinylpyrrolidone solution (PVP, Life Global, USA) was put in the center of a Falcon 1006 ICSI plate coated with heated mineral oil, and sperm was added (mineral oil, Life Global, USA). Testicular sperm motility was evaluated, and Pentoxifylline (PF) was administered if necessary. The sperm injection was performed on a 37°C inverted microscope stage heater. After 30 minutes, post ICSI for the cases included in group (I), the oocytes for each patient were randomly divided into two groups: Group A (with activation) and group B (without activation). After washing, the oocytes were put in the same incubator with fertilization media (Global Total LGGT, Life Global, USA). Oocytes from each patient in group (II) were further randomly divided into two distinct groups: Group A (with activation) and group B (without activation). The oocytes were then washed and incubated.

Normal fertilization was determined by the existence of two pronuclei between 16 and 18 hours post-ICSI, at which point the embryo was examined for signs of development. After 48 hours of fertilization, the viability and quality of the embryos were assessed.

Statistical analysis:

For numerical variables, the results were presented as a mean SD. Depending on the sample size, Student's *t*-test was used to compare means, while the chi-squared test was used to compare percentages.

Results

In this randomized controlled study, 76 ICSI cycles were included and done at The Egyptian IVF-ET center between May 2018 and October 2019. Female partners had a mean age of 29.9 ±11.7. The infertility period mean was 6.8 ±4.3 years. In 51 cycles, spermatozoa were collected from ejaculated semen, and in 24 cycles, spermatozoa were collected from testicular biopsies. Sperm counts varied widely, from a few spermatozoa to $30x\ 10^6$/mL, with a mean of $8 \pm 4x\ 10^6$/ml. The abnormal forms made up between 98-100%, whereas mobility varied from 0 to 30%. The mean age of the male was 36.8 years old.

The included 76 ICSI had 868 oocytes that randomly divided into two groups; the electroactivated group with 414 oocytes and the control group with 454 not activated oocytes. As a result of electroactivation, the fertilization rate was statistically significantly higher in the treatment (electroactivated) group than in the control group (61.8% vs. 40.8%; odds ratio = 1.465; 95% confidence interval = 1.187 to 1.529; p<0.0001). The incidence of oocyte degeneration was similar across the two groups (0.9% vs. 0%, odds ratio = 0.96, 95% confidence interval = 0.73-1.26). Three cycles (2.6%) in both groups had TFF, while 17 cycles (22.4%) experienced partial fertilization failure (in the control group), meaning that 17 cycles (15 patients) would have lost their opportunity of embryo transfer and probable pregnancy if elec-

troactivation had not been undertaken. In contrast, partial failure of fertilization occurred in 6 cycles (7.9%) in the electroactivated group where four of the 6 cycles had fertilized oocytes in the control group (Table 1).

The included 76 ICSI were randomly divided into two groups; the first group included the oocytes that were electroactivated 2 hours post ICSI (42 cases had 482 oocytes, 216 oocytes activated and 266 as control), and the second group was with those electroactivated immediately within 30 minutes post ICSI (34 cases had 386 oocytes, 198 oocytes activated and 188 as control). Comparison of the 2 groups reveled that the first group had-significantly higher fertilization rate than the second group (70.4.8% vs. 52.5%; odds ratio = 1.465; 95% confidence interval = 1.187 to 1.529; $p<.0001$). Partial fertilization failure occurred in the oocytes activated after two hours in two cycles (4.7%) while four cycles (11.8%) had the same failure in the oocytes activated within half hour (Table 2).

Table (1): Effect of electroactivation on the fertilization & degeneration rate on sibling oocytes of 76 ICSI cases.

Parameter	Electroactivation group	Control group
Number of metaphase II oocytes	414	454
Fertilization Rate **a**	61.8%	40.8%
Degeneration Rate **b**	0.9%	0%

aOdds ratio = 1.465; 95% confidence interval = 1.187 to 1.529; $p<0.0001$).
bOdds ratio = 0.96; 95% confidence interval = 0.73 to 1.26).

Table (2): Oocyte electroactivation post ICSI: Two hours vs immediate (within 30 minutes) activation.

Parameter	2 hours	Immediate (within 30 minutes)
Number of cycles	42	34
Number of activated oocytes	216	198
Fertilization Rate **a**	70.4%	52.2%
Partial Fertilization Failure	2 cycles (4.7%)	4 cycles (11.8%)

- **a**70.4.8% vs. 52.5%; odds ratio = 1.465; 95%; confidence interval = 1.187 to 1.529; $p<.0001$.

Discussion

Despite the success of ICSI technique to overcome the most difficulties associated with male-factor infertility cases, poor fertilization and a total failure of fertilization still can occur in about 2-3% of all ICSI cycles and can reappear in subsequent cycles **[4]**.

The goal of AOA is to artificially increase intracellular $Ca^{2}+$ levels in the oocyte in order to restart the meiotic process. AOA can be induced by mechanical, electrical, chemical, or a hybrid of these stimuli, each of which carries its own set of hazards and advantages. By applying a direct voltage current, electrical activation causes the movement of charged lipid bilayer proteins and the development of membrane pores, which in turn allows external $Ca^{2}+$ to enter the oolemma. Mechanical activation typically entails micromanipulative oolemma piercing, followed by strong cytoplasmic aspiration utilizing a modified ICSI method, evoking a $Ca^{2}+$ influx, and finally ICSI. Microinjecting $Ca^{2}+$ into the oocyte is another mechanical activation approach. Such techniques, however, are not likely to be standardized, and like other physical techniques, they will only result in a single $Ca^{2}+$ rise. $Ca^{2}+$ ionophores, on the other hand, are lipid-soluble compounds that may transport $Ca^{2}+$ through the oolemma, increasing $Ca^{2}+$ permeability and inducing external $Ca^{2}+$ inflow, and eliciting internal $Ca^{2}+$ storage to release stored $Ca^{2}+$, thereby mediating chemical activation **[9]**.

In our study of 76 cycles with severe oligoteratoasthenospermia or nonobstructive azoospermia with total teratospermia or totally immotile spermatozoa, total fertilization failure (TFF) occurred in two cycles (2.6%) in both the control group and the electroactivated group, while partial failure of fertilization occurred in 17 cycles (22.4%) in the control group and 6 cycles (7.9%) in the electroactivated group.

This result ensures the role of the injected spermatozoon in activating the oocyte to complete meiosis and normal viable spermatozoa is needed to achieve that. Total teratozoospermia or oligoteratoasthenospermia are the most common causes of fertilization failure after ICSI, suggesting that structural abnormalities may be associated with the deficiency of oocyte-activating factors even if it is not yet clear whether sperm morphology has a direct relation to DNA damage or not.

Achieving fertilization rate of 61.8% in the electroactivated group along with having normal (although limited) fertilization rate in 17 cycles (15 patients), those who had partial failure of fertilization in the control group, are a good proof that electroactivation is a real rescue in such cases to get embryos for subsequent transfer. However, in 4 cycles that had fertilized oocytes in the control group and not in the electroactivated group may indicate that splitting the oocytes is a much safer option.

Comparing the fertilization rates in the group that included the oocytes electroactivated 2 hours after injection with those electroactivated within half hour after injection gives more credit for applying electroactivation in 2 hours after injection as a standard option in IVF labs that is using electroactivation technique as their tool of choice in artificial oocyte activation.

In another hand, calcium ionophores have been found to increase the fertilization rate of artificial oocytes by 69.4% when used with ejaculate-retrieved spermatozoa, 48.9% when used with epididymis-retrieved spermatozoa, and 50.6% when used with testicular sperm **[10]**.

In contrast, other reports that agree with this study dictate that it has not yet been proven which method of oocyte activation is the most efficient and safest method foro ocyte activation in humans. Many findings show that the fertilization and pregnancy rates can be considerably improved by using ICSI in conjunction with AOA **[11-17]**, while recent meta-analysis suggest that ionophore therapy significantly increased clinical pregnancy rates and oocyte activation **[18]**. This, however, contradicted a previous meta-analysis that found the opposite to be true **[19]**.

In conclusion, and according to this study, artificial oocyte activation using electroactivation technique after ICSI significantly improved fertilization and may be useful in selected patients who have low fertilization potential as in cases of previous failure of fertilization or limited fertilization, as well as in cases of severe oligoasthenospermia or azoospermia with 100% abnormal forms or zero motility.

Performing electroactivation in 2 hours after ICSI resulted in a better fertilization rate compared to directly or within 30 minutes electroactivated cases, such result if applied may lead to a better fertilization outcome in lab practice.

Further studies are required to further validate these findings and to establish the biosafety of artificial oocyte activation. Clinical tests are needed to evaluate the activation potential of semen samples for proper patient selection and to investigate the best method of oocyte activation to be used for better results in total/limited fertilization failure cases.

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هل يمكن لتوقيت تقنية التنشيط الكهربائى للبويضات أن تؤثر على نسبة الأخصاب لدى البويضات بعد عملية الحقن المجهرى؟

الخلفية العلمية : يعد فشل أخصاب البويضات بعد عملية الحقن المجهرى من أهم أسباب البحث فى أسباب هذه النتيجة المؤسفة منذ إكتشاف تقنية الحقن المجهرى. البحث فى جذور المشكلة وخاصة تلك المرتبطة بالعقم الناتج من العامل الذكرى قد تمت بشكل كثيف فى العقد الماضى لأهميتها. أحد الجهود المبذولة للتغلب على هذه المعضلة هو تقديم تقنية التنشيط الاصطناعى للبويضات بعد عملية الحقن المجهرى.

الهدف : لمعاينة تقنية التنشيط الكهربائى الاصطناعى للبويضات والأثر المترتب على الأوقات المختلفة فى عمليات الحقن المجهرى فى حالات ضعف الخصوبة الشديدة ذات العامل الذكرى.

تصميم البحث : دراسة مُحكمة عشوائية مستقبلية.

أعداد البحث : المر كز المصرى لأطفال الأنابيب (مركز خاص للأخصاب المساعد فى مصر) بالتعاون مع معهد الهندسة الوراثية والتكنولوجيا الحيوية بجامعة مدينة السادات.

المرضى : ستة وسبعون مشارك تم اختيارهم لهذه الدراسة، جميعهم كانوا يعانوا من إما قلة عدد الحيوانات المنوية مع ضعف حركتها وعدم طبيعة شكل هذه الحيوانات المنوية أو انعدام الحيوانات المنوية مع عدم وجود حاجز فى مجرى القذف مع عدم طبيعة شكل الحيوانات المنوية بشكل كامل إن وجدت أو انعدام حركة الحيوانات المنوية بشكل كامل. وأيضاً تم إدخال المرضى الذين لم يحدث لهم اخصاب للبويضات بشكل كامل أو بشكل جزئى بعد عملية حقن مجهرى سابقة.

التدخل : بعد عملية سحب البويضات وجمعها (العدد الكلى = ٨٦٢ بويضة من ٦٧ مريض) تم تقسيمهم بشكل عشوائى بعد عملية الحقن المجهرى إلى مجموعتين : مجموعة الدراسة الأولى أ (وعددها ٤٠٨) عُرضت إلى التنشيط الكهربائى والمجموعة الضابطة الثانية ب (وعددها ٤٥٤) لم تُعرض إلى تنشيط كهربائى. الحالات التى تم ضمها فى مجموعة الدراسة الأولى أ تم أيضاً تقسيمها إلى مجموعتين المجموعة ١ والتى تضمنت الحالات التى تم تنشيطها فى خلال ٣٠ دقيقة من بعد عملية الحقن المجهرى مباشرة (وعددها ٣٤)، بينما كانت المجموعة ٢ والتى تضمنت الحالات التى تم تنشيطها كهربائياً عند الساعة الثانية من عملية الحقن المجهرى (وعددها ٤٢).

مقياس النتيجة الأساسية : نسبة الأخصاب وسنسبة الانحلال.

النتائج : ستة وسبعون حالة حقن مجهرى تم ضمهم إلى هذه الدراسة .

المجموعة التى تم تنشيطها بالكهرباء كان لديها نسبة إخصاب أعلى من المجموعة التى لم تتعرض للتنشيط الكهربائى (المجموعة الضابطة) بنسبة ٦٣٪ مقابل ٤١٪ على التوالى. نسبة الإنحلال للبويضات لم تكن مختلفة إحصائياً بين المجموعتين بنسبة ١٪ مقابل ٠٪ على التوالى. بينما كانت نسبة الإخصاب أعلى إحصائياً فى المجموعة ١ (المنشطة خلال ٣٠ دقيقة) عن المجموعة ٢ (المنشطة عند الساعة الثانية) بنسبة ٧٠٪ مقابل ٥٢٪ على التوالى. لم يتم ملاحظة أى فرق إحصائى هام بين المجموعتين فيما يتعلق بنسبة الإنحلال للبويضات بنسبة ٠.٠٥٪ مقابل ٠.٠٤ وبالرغم من نتاج فشل إخصابى كامل فى ١٥ حالة فى المجموعة الضابطة وفى ٦ حالات فى مجموعة الدراسة إلا أن الفشل الاخصابى التا م ظهر فى ٣ حالات فقط وتم إلغاء عملية ارجاع الأجنة للرحم.

الاستنتاج : بعض من المرضى المختارين والذين يعانون من مقدرة إخصابية محدودة قد يكون لهم استفادة من عملية التنشيط الاصطناعى للبويضات باستخدام التنشيط الكهربائى. استخدام التنشيط الكهربائى عند ساعتين بعد عملية الحقن المجهرى كان لها أثر أفضل فى نسبة الاخصاب مقارنة بالتنشيط الكهربائى فى خلال ٣٠ دقيقة فى المجموعة التى تم تنشيطها فى هذه الدراسة. إن تم استخدام هذه النتائج قد نشهد تحسن فى نسبة الاخصاب للبويضات فى العمل اليومى فى معامل الأجنة.