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Spermic Toxicity Test of Medical Devices for Assisted Reproductive Technology

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Abstract: China has been putting great effort to promote the human assisted reproduction technology (ART) but impose a stringent regulation over the market at the same time. Thus, the safety and effectiveness tests at pre-clinical stage became even more important. Human sperm toxicity test can be used to evaluate the potential effects ART products have on human gametes. To provide a thorough summary and analysis over sperm toxicity evaluation of medical devices for ART operation, as well as to forecast its future direction, currently available test methods and evaluation indicators related to human sperm were elaborated here. However, no test can apply for all kinds of products. It especially holds water in ART field. Not mention the resource of human sperm is scarce worldwide. Thus, this method's weakness and risk points were stated. Besides, possible alternative approaches for further improvement were also provided. The main purpose of pre-clinical tests and the market supervision never is to impede the progress of the industry, but to provide a reliable and robust system that cultivates competent and creative researchers as well as companies. Ultimately, by pulling government, hospital and industry together, we are able to achieve the primal goal of ART, happily having healthy offspring.

Keywords: Assisted Reproductive Technology, Medical Devices, Human Sperm Survival Assay

1. Introduction

Accompanied with a surging need of human assisted reproductive technology, the development of assisted reproductive medical devices emerges in an endless stream, which covers all kinds of media and appliances that have directly or indirectly contact with sperm, oocytes or embryos. However, to ensure the health of our offspring, a thorough study on the potential toxicity is essential for ART products. Thus, sperm toxicity test is an indispensable part in the safety and effectiveness evaluation of such products. The Chinese industrial standard YY / T 1535 specifies the relevant details [1] of human sperm survival test, but the specific indicators and detection methods need to be further explored for products served for purposes such as sperm selection, sperm freeze and so on. In this paper, we elaborated currently available methods as well as their scientific principles. However, the shortage of high-quality sperms has been a main problem in clinical, not mention to use such valuable resource in pre-clinical tests. Thus, to speed up the product inspection process, avoid the waste of human sperm resources and cumbersome procedures such as ethical review, human sperm replacement test is also worthy of attention, which has also been discussed here.

2. The Purpose, Available Methods and Future of Spermic Toxicity Test

2.1. Types, Risks and Regulation of Human Assisted Reproductive Technology and Related Medical Devices

Human assisted reproduction technology (ART) emerged in the 1970s, which applies medical technology to manually operate gametes, zygotes and embryos, and gave hope of pregnancy to infertile couples. ART covers artificial insemination (AI) and in vitro fertilization-embryo transfer

(IVF-ET) technology and various derivative technologies [2-4]. According to the World Health Organization (WHO), the incidence of infertility in developed countries was about 5%~8%, in some areas of developing countries the percentage can reach 30%, while China was about 15% [5-6]. As a crucial part of human reproductive health services, ART has been rapidly developed and improved worldwide in recent years.

ART related medical devices mainly include various culture media, washing buffers, freezing products, as well as various culture dishes, egg collecting needles, microinjection needles and embryo transferring tubes. These products have direct or indirect contact with human gametes and / or embryos during ART operation, so infertile patients are exposed to great uncertainties while using them. Not mention these products not only affect the patients, but also the health and developmental safety of their offspring [7-8]. To sum up, we cannot emphasize the importance of imposing stringent supervision on such products to ensure the health of the people.

In fact, most countries have attached great importance to ART-related medical devices and established a specialized regulatory system. Since 2001, the ministry of health in China successively issued *the measures for human assisted reproductive technology management*, *the measures for the administration of human sperm bank* and t*he basic standards and technical specifications for human sperm bank*. Then, serials of national and industrial standards were carried out to further standardize the clinical application of assisted reproductive technology [9-11]. However, most Chinese market share of liquid ART products were occupied by imported products. The domestic enterprises are still in their infancy state but grow rapidly. Most domestic products are undergoing the application process of registration inspection. Besides, our country is promoting the standardization of human assisted reproductive technology as well as corresponding medical devices. Thus, the research and utilization of domestic ART products is ever more necessary [12-14].

2.2. Safety and Functional Testing for Human Sperm

2.2.1. Human Sperm Survival Test Suits for the Safety Test of Most ART Products

The safety evaluation of ART medical devices often requires tests of their impacts on human gametes (such as sperm) because of their clinical usage. In 2017, the State Food and Drug Administration issued *the Human Sperm Survival Test for Biological Evaluation of In Vitro Assisted Reproduction Medical Devices* (*YY / T 1535-2017*) [1] to evaluate the possible toxicity risk of media and appliances that are in direct contact with sperm, oocytes or embryos in ART process. Human sperm survival test requires using of human sperm, thus the person who carry on the test must be qualified and have permission to such resources. The test article or its extract was co-incubated with the human sperm for 24 hours, and then the change of sperm motility was measured and calculated to indirectly evaluate whether products are potentially toxic to sperms, eggs, or embryos. The sperm motility was represented by the percentage of forward motion sperm (FM) accounted for all sperm (the sum of sperms with forward movement (FM), the immobilized (IM) and non-forward movement (NF)) in the field of microscope, namely:

$$\text{Sperm Motility} = \text{FM}/(\text{FM}+\text{IM}+\text{NF})\times 100\% \quad (1)$$

However, it is worth noting that such test is not applicable for the detection of sperm freeze buffer (which causes a significant decrease in sperm motility), products with hyaluronidase (which affects sperm membrane and then affects sperm motility), and so on.

2.2.2. Functional Tests Customized for Special Products with Human Sperm

As for testing ART products' potential toxicity towards gametes, mouse embryo test can be used instead of human sperm test. [15] However, for products with specific purpose such as gradient separation, their performance indicators should also be added according to validate corresponding functions. Relevant functional tests and respective standards remain blank for most of such products. The Guiding Principles for Technical Review of Registration of Human In Vitro Assisted Reproductive Technology suggested that the density index [16] should be set for sperm gradient separation fluid and oil products. At the same time, such products were used for selecting energetic sperms, the recovery rate of active sperm and the sperm motility rate after processing should also be taken into consideration [17, 18].

Sperm motility improvement test is based on the survival test, by mimicking the clinical use of sperm selecting products, therefore, to study the difference of sperm motility before and after the treatment with the testing products. The sperm motility improvement rate was calculated using the formula below:

$$\text{Motility Improvement Rate} = \text{Sperm Motility after Treatment} - \text{Sperm Motility before Treatment} \quad (2)$$

Naturally, only using motility improvement rate to evaluate relevant products is insufficient. If the number of sperm after treatment dropped dramatically, such product would not meet the requirements of clinical use. Thus, the effectiveness of the product is also questionable [19-22]. To solve this problem, we added another indicator, active sperm recovery rate, which can be calculated by using formula below:

$$\text{Sperm Recovery Rate} = \text{Sum of Sperm after Treatment}/\text{Sum of Sperm before Treatment}\times 100\% \quad (3)$$

With these two indicators, the effectiveness of sperm selecting products can be described more comprehensively.

Another product category is sperm immobilization products, which is used to artificially reduce sperm motility during microscopic operation, so the evaluation methods and

indicators should be adjusted accordingly [23]. It should be noted that the parameter we chose at this time is sperm activity rather than sperm motility. Because sperm motility is only a percentage that forward moving sperms account for all sperms during observation, which is not enough to describe the sperm activeness [24-25]. Sperm activity generally represent the velocity of sperm movement, which can be measured visually by the microscope combined with the counting plate, or the computer-assisted analysis system (CASA), which provides more objective measurements [26-28]. However, like sperm selecting products, the immobilization performance of sperm immobilization products can be evaluated by the sperm activity or sperm immobilization rate after the product treatment, namely:

$$\text{Sperm Immobilization Rate} = \text{Sperm Activity after Treatment} / \text{Sperm Activity before Treatment} \times 100\% \quad (4)$$

These functional tests can validate not only the safety but also the effectiveness of the corresponding products, so they are major research directions for future method development.

2.2.3. Exploration of Alternative Methods for Human Sperm Testing

The emergence of ART changed the traditional way of fertility, as it benefited so many infertile couples, also brought many ethical and social legal problems. Sperm carries the half genetic information and has potential to developed into a complete individual. Thus, any usages that involves sperm often need to get multiple permission from ethical committee [9-11]. The review process is lengthy and tedious. Moreover, the sperm shortage is always a major concern in China. In the case of the limited number of sperm donors, many infertile families still wait for proper sperm resources. Therefore, using human sperm for such pre-clinical tests could be a waste of resources [29-31]. At this point, looking for an alternative animal model has become a new trend. As common domestic animals, using pigs and rabbits is relatively feasible. Their sperms' external morphology is not significantly different from that of human sperm. They all have clear sub-structures like head, neck and tail [32-33]. According to the previous research, the head/neck length ratio of pig and cattle sperms is similar to that of human sperm, but difference of tail length is relatively greater. In particular, pig sperm has been used in many methods optimization articles about sperm selecting as well as sperm velocity measurement. The operation process is basically consistent with the ART process in clinic, and the test conclusion is also generalized [34-36]. Thus, pig sperm can be an alternative biomaterial for human sperm. However, because its animal origin, validation processes such as pathogen removal were required, and a more comprehensive comparison between human sperm needs to be completed. [37]

3. Conclusion

With the development of assisted reproductive technology in the world, China's related technologies and standardization system have also made great progress. However, we all admitted that there is still a large gap of building a complete standard system. For example, there is no industrial standard for the safety and functional tests of human sperm selecting products as well as immobilization products. We developed several functional tests to make up for the limitation of sperm toxicity test. Most of them using sperm motility or sperm activity as main parameters of evaluation, so a computer-aided analysis system (CASA) can not only save time but produce more objective results. In addition, when it comes to human sperm test, ethical issues cannot be avoided, so further exploration of human sperm replacement test will also be an important direction of product toxicity evaluation for assisted reproductive technology in the future.

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