INPLASY PROTOCOL

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Corresponding author:
Yijin Pei

pyj@gdmu.edu.cn

Author Affiliation:
Guangdong Medical University.

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Conflicts of interest:
None declared.

The Efficacy of Stem Cell Transplantation for Azoospermia in Animals: A Systematic Review and Meta-analysis

Qiu, JX[1]; Ma, HF[2]; Mai, PJ[3].

Review question / Objective: **The aim of this meta-analysis is to investigate the efficacy of SCT for Azoospermia, in order to determine the most effective therapeutic regimen of SCT on azoospermia, we performed the meta-analysis comparing the efficacy of multiple differences that appeared in different SCT (e.g., transplantation method, injection site, induction of azoospermia, and stem cell type), respectively.**
Information sources: **Data as followed were extracted from retrieved studies: (1) authors; (2) publication year; (3) country; (4) azoospermia animal species; (5) cell sources; (6) injection site and injection dose; (7) induction of azoospermia; (8) number of animals each group and (9) outcomes: expression level of three meiosis-related genes and hematoxylin-eosin positive staining area percentage of testes. Tools for information extraction included Image-Pro Plus 6.0 and WebPlotDigitizer 4.5 were used in extracting graphed data.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 June 2022 and was last updated on 13 June 2022 (registration number INPLASY202260056).

INTRODUCTION

Review question / Objective: **The aim of this meta-analysis is to investigate the efficacy of SCT for Azoospermia, in order to determine the most effective therapeutic regimen of SCT on azoospermia, we performed the meta-analysis comparing the efficacy of multiple differences that appeared in different SCT (e.g., transplantation method, injection site, induction of azoospermia, and stem cell type), respectively.**

Condition being studied: **Infertility is a common clinical condition affecting approximately 48.5 million couples worldwide that characterized by the failure**

to clinical pregnancy with at least 12 months of regular and non-contraceptive sexual activity. WHO estimates that male factor being a primary or contributing cause in approximately 50% of infertile couples, which is a substantial and noticeable index. There are many forms of male factor infertility, of which azoospermia is the most severe form that occurring in almost 15% of infertile men. According to different pathogenesis, azoospermia can be divided into two categories: non-obstructive azoospermia (NOA) and obstructive azoospermia (OA). NOA is caused by testicular abnormalities resulting in inadequate production of spermatozoa and therefore more difficult to treat. Moreover, NOA can be subdivide mainly into idiopathic NOA and NOA with a history of cryptorchidism, that can pass on to the next generation due to chromosomal gene deletion or induce testicular cancer, respectively. At present, sperm donation and assisted reproductive technique are the most available treatment to infertile male patients. However, these methods are not suitable if no spermatozoa can be retrieved from the testicle exactly as NOA patients. Hence, the clinical demand for alternatively effective therapy is urgent.

METHODS

Search strategy: Three databases (PubMed, EMbase, The Cochrane library) were systematically searched for original articles. The search terms consist of free words and MeSH terms included "Stem Cell Transplantation" or "Stem Cells" and "Azoospermia". Studies dated from January 2006 to February 2022 were all included.

Participant or population: Serveral azoospermia animal models were included. Among all the studies included in this meta-analysis, 11 studies used mouse models, 5 studies used rat models, 2 studies used hamster models and 1 study used guinea pig models.

Intervention: Azoospermia animal models in experimental group received stem cell therapy.

Comparator: Azoospermia animal models in control group did not received stem cell therapy.

Study designs to be included: Study that used animal models will be include irrespective of language or country.

Eligibility criteria: Articles were excluded if: (1) the study presented only an abstract; (2) the study was a review, editorial, reply letter or note; (3) the study has no available or incomplete data and (4) the study has no available full-text article. Studies were eligibly included if they fulfilled the criteria as followed: (1) the study was carried out on azoospermia animal models; (2) azoospermia models in experimental group received stem cell therapy; (3) a control group composed of the same animal model was designed and (4) the data regarding one or more of the following outcomes related to azoospermia healing could be extracted: expression level of deleted in azoospermia like (DAZL) gene, expression level of synaptonemal complex protein 3 (SYCP3) gene, expression level of DEAD-box helicase 4 (VASA) gene or average hematoxylin-eosin positive staining area percentage of testes.

Information sources: Data as followed were extracted from retrieved studies: (1) authors; (2) publication year; (3) country; (4) azoospermia animal species; (5) cell sources; (6) injection site and injection dose; (7) induction of azoospermia; (8) number of animals each group and (9) outcomes: expression level of three meiosis-related genes and hematoxylin-eosin positive staining area percentage of testes. Tools for information extraction included Image-Pro Plus 6.0 and WebPlotDigitizer 4.5 were used in extracting graphed data.

Main outcome(s): The expression level of three meiosis-related genes and hematoxylin-eosin positive staining area percentage of testes.

Quality assessment / Risk of bias analysis: SYRCLE's risk of bias tool for animal studies was used to assess the risk of bias

of the included studies. This tool is an adapted version of the Cochrane risk of bias tool specifically for animal intervention studies which contains 10 entries related to 6 types of bias: sequence generation (selection bias), baseline characteristics (selection bias), allocation concealment (selection bias), random housing (performance bias), blinding (performance bias), random outcome assessment (detection bias), blinding (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias (other biases). Each entry will be judged with one of the three different judgments: “low risk”, “high risk” and “unclear risk”.

Strategy of data synthesis: The meta-analysis was performed using Review Manager version 5.2 software provided by the Cochrane Collaboration. For articles that present only graphed or imaged data, two independent authors extracted mean and standard deviation (SD) values from graphs and images using tools. A random-effect model was used for the analysis and the standard mean difference (SMD) with 95% confidence intervals (CI) were considered as the pooled effect of outcomes. The significance set at $P<0.05$, and heterogeneity values were calculated while using I2 to quantify heterogeneity. If $I2>50\%$, heterogeneity was deemed to be substantial.

Subgroup analysis: Subgroup analysis were performed if necessary according to transplantation method, injection site, induction of azoospermia, azoospermia animal species and cell sources to find potential source of heterogeneity. Heterogeneity for subgroup analysis was assessed using I2. Graphical funnel plot was used to investigate possible publication bias.

Sensitivity analysis: Analysis model: if $I2>50\%$, heterogeneity was deemed to be substantial and analysis model was changed to random effects.

Language: No language restriction in this meta-analysis.

Country(ies) involved: This meta-analysis is carried out in China, all authors' nationalities are China.

Keywords: stem cell transplantation; azoospermia; Image-Pro Plus; Meta-analysis.

Contributions of each author:

Author 1 - Jiaxin Qiu.
Email: 527881992@qq.com
Author 2 - Huifen Ma.
Author 3 - Peiju Mai.