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META-ANALYSIS

Phosphodiesterase-5 Inhibitors in Reversal of Male Infertility: A Meta-Analysis

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ABSTRACT

The prevalence of male infertility is an increasing concern in the domain of public health, impacting a substantial number of men globally.Phosphodiesterase-5 (PDE-5) Inhibitors primarily used for the treatment of erectile dysfunction. This Meta-analysis has been done to investigate the success rate of the drug Phosphodiesterase-5 Inhibitors therapies in reversal of infertility in the men. We conducted an extensive review of multiple databases to gather research examining effects of diverse pharmacological agents on male fertility factors. Our selection focused on robust study design, namely randomized controlled trials, observational studies, and clinical trials, which evaluated the success of the drugs relative to placebos or no treatment. To perform Meta-analysis total number of 220 research papers were systematically reviewed; apart from the 220 research papers 20showed more similarity to our topic efficacy of drug Phosphodiesterase-5 Inhibitors in the reversal of male infertility.This Meta-analysis suggests that Phosphodiesterase-5 Inhibitors can positively impact in the treatment of erectile dysfunction. These findings indicate that Phosphodiesterase-5 Inhibitors may be a valuable therapeutic option for certain types of male infertility. This meta-analysis offers a comprehensive synthesis of current evidence and suggests areas for future research to confirm drug Phosphodiesterase-5 Inhibitorsrole in the treatment of male infertility.

KEY WORDS: Phosphodiesterase-5 Inhibitors, erectile dysfunction, male infertility

INTRODUCTION

Fertility is the capacity of an individual or couple to produce children naturally; it is typically assessed by the individual's ability to conceive and have a successful pregnancy. Fertility may be impacted by a variety of factors, including genetic, environmental, and biological ones (Mateu *et al*., 2010). The genetic materials of two parentscombined during sexual reproduction, resulting in children with a unique genetic makeup (Heitman *et al*., 2013). Infertility is defined as the inability of a couple to conceive after a year of consistent, unprotected sexual activity which is a major social issue in many nations due to the impact of lifestyle on reproductive health. It is associated with several stressors that might affect a man's ability to engage in sexual activity (Song *et al*., 2021). Also, it is linked to environmental factors including heat, insecticides, and lifestyle factors like stress, nutrition, smoking, and other factors that affect fertility (Levine *et al*., 2017). According to the World Health Organization (WHO), male infertility is the inability of a sexually mature man to conceive a fertile woman (Leaver, 2016). Approximately one-third of all cases of infertility are caused by male reproductive issues (Olayemi, 2010). The inability to conceive a child is the primary indicator of male infertility. In addition to preventing unintended pregnancies, effective contraception promotes shared responsibilities in infertility (Sedlander *et al*., 2018). Low sperm count, decreased sperm motility, or irregular sperm shape are frequently associated with infertility in men (Upadhyay *et al*., 2020).

A common illness known as erectile dysfunction causes men to struggle to get or keep an erection strong enough for sexual performance (Potts *et al*., 2006). Several lifestyle factors, obesity, and a decrease in physical activity are among the non-traditional causes of erectile dysfunction, in addition to classic conditions including diabetes and hypertension (Shamloul *et al*., 2005). Hypertension, excessive cholesterol and atherosclerosis

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can all reduce blood flow to the penis, high suger level can damage the nervous and blood vessels, low level of testosterone also cause erectile dysfunction (Chowdhury *et al*., 2019). The worries of men about performance, employment, or personal issues can impair sexual function, relationship issues, communication issues, and unsolved arguments with a spouse might lead to erectile dysfunction (McCabe *et al*., 2010).

Erectile dysfunction (ED) is commonly treated with a class of drugs called Phosphodiesterase-5 (PDE-5) Inhibitors. The most well-known PDE-5 Inhibitors are Vardenafil (Levitra), Tadalafil (Cialis), and Sildenafil (Viagra) (Aversa *et al*., 2006). Sildenafil is the first oral selective Phosphodiesterase-5 Inhibitor, introduced in 1998, significantly advancing the pharmacological treatment of end-stage renal diseases (Afsar *et al*., 2015). Sildenafil was swiftly adopted by the medical profession and the general public due to its broad efficacy in treating many types of end-stage renal disease and ease of use (Campbell, 2005). Phosphodiesterase-5 Inhibitors are now considered the standard treatment for treating erectile dysfunction (Lombardi *et al*., 2012). They mainly improve blood flow to the penis which relaxes smooth muscles and enlarges blood vessels in the corpus cavernosum (Lue, 2000). PDE-5 Inhibitors may be useful in treating male infertility in certain circumstances. Their main use is for erectile dysfunction (Isidori *et al*., 2014). PDE-5 Inhibitors help men with erectile dysfunction achieve and sustain erections, which are essential for a spontaneous pregnancy (Mostafa, 2008). This is particularly crucial for males whose infertility is caused by erectile dysfunction rather than sperm quality (Zhang *et al.,* 2019). Vardenafil is a potent and selective PDE-5 Inhibitor that has been shown to have a quick initial reaction, prolonged effectiveness, and reliability in the treatment of erectile dysfunction. Vardenafil is helpful in the general population of males with erectile dysfunction (Montorsi *et al*., 2004). We conducted a systematic review and meta-analysis to provide an overview of the published studies on the efficacy of the drug Phosphodiesterase-5 Inhibitors in reversing male infertility.

MATERIALS AND METHODS

In this study, the systematic approach was used to conduct a Meta-analysis for evaluating the efficacy of Phosphodiesterase-5 Inhibitors in reversing male infertility in order to clarify the effectiveness of these treatments and inform clinical decision-making regarding male infertility management.

Search Strategy

The electronic databases were searched for relevant studies by using online platforms including PubMed, MEDLINE, Cochrane Library, Embase, Web of Science, and Google Scholar.A combination of different keywords and Medical Subject Headings such as PDE-5 Inhibitors, Male Infertility, Male Sterility, Male Reproductive Health, and Erectile Dysfunction were used for searching research articles. It was performed through the following search limitations, studies published in English will be included. Studies published from [2000] to [2018] for Phosphodiesterase-5 Inhibitors will be considered.

Inclusion/Exclusion Criteria

Inclusion was done based on studies that evaluate the efficacy of Phosphodiesterase-5 Inhibitors in treating male infertility, randomized controlled trials (RCTs) or observational studies (cohort, case-control). Exclusion Criteria included studies not focusing on Phosphodiesterase-5 Inhibitors, non-human studies, reviews, editorials, commentaries, and case reports, and studies with insufficient data on efficacy outcomes.

Data Extraction

To perform Meta-analysis total number of 220 research papers were systematically reviewed; apart from the 220 research papers 20 showed more similarity to our topic efficacy of drug Phosphodiesterase-5 Inhibitors in reversing male infertility. So, we include data from 20 research papers for this Meta-analysis.

Statistical Analysis

Random-effects models were used due to expected heterogeneity among studies. Effect sizes were calculated using standardized mean differences (SMD) or odds ratios (OR) with 95% confidence intervals (CI). Heterogeneity was assessed using the I^2 statistic and Chi-square test. Funnel plots and Egger's test are used to assess potential publication bias.

RESULTS

Fixed and Random Effects of PDE-5 Inhibitors for Control and Experimental Group

For control group, the result of the Meta-analysis indicated that the "Q" value 20.143 with degrees of freedom (df) of 1 and a p-value of <0.001 indicates a significant omnibus test of model coefficients. This suggests that there is an important overall effect in the Meta-analysis. On the other hand, the "Test of Residual Heterogeneity" shows a value of 307.405 with 19 degrees of freedom and a P-value of <0.001. This indicates that there is significant residual heterogeneity among the studies included in the Meta-analysis. The results suggest that there is a significant overall effect in the model coefficients being tested, but there is also significant variability or

heterogeneity among the individual study results. The findings from these tests are crucial for interpreting the results of the Meta-analysis and drawing meaningful conclusions about the efficacy of Phosphodiesterase-5 Inhibitors in the reversion of male infertility (Table 1).

Table 1: Classical Meta-analysis with fixed and random effects among multiple studies on efficacy of drug Phosphodiesterase-5 Inhibitors in reversing male infertility for control group

Fixed and Random Effects (control group)			
	Q	Df	P
Omnibus test of Model Coefficients	20.143	1	< .001
Test of Residual Heterogeneity	307.405	19	< .001

P -values are approximate.
The model was estimated using Restricted ML method.

For the experimental group, Omnibus test of Model Coefficients showed a significant result with a high Q value of 20.908 and a p-value of <0.001, indicating a strong overall model fit. The Test of Residual Heterogeneity further supported the findings, with a significant result showing residual variability in the data with a Q value of 628.826 and a p-value of <0.001. The model estimation was performed using the Fixed Effects method, which assumes that all studies in the Meta-analysis share a common effect size. This method is commonly used when there is low heterogeneity among the included studies, allowing for a more precise estimation of the overall effect (Table 2).

Table 2: Classical Meta-analysis with fixed and random effects among multiple studies on efficacy of Phosphodiesterase-5 Inhibitors in male infertility for experimental group

Fixed and Random Effects (experimental group)			
	Q	Df	P
Omnibus test of Model Coefficients	20.908	1	<.001
Test of Residual Heterogeneity	628.826	19	<.001

P -values are approximate.
The model was estimated using Restricted ML method.

Parameter Covariance of efficacy of Phosphodiesterase-5 Inhibitors in Reversing Male Infertility for Control and Experimental Groups

In the present study of meta-data, various statistical estimates and tests related to residual heterogeneity, parameter covariance, and tests for funnel plot asymmetry are presented. These values provide insights into the variability and relationships within the data being analyzed. The τ^2 and τ estimates indicate the amount of heterogeneity present in the data, while I^2 and H^2 provide information on the percentage of variability that can be attributed to heterogeneity. The parameter covariance for the intercept shows the relationship between intercept values. The rank correlation test and regression test assess asymmetry in the funnel plot, with Kendall's τ and Egger's test providing measures of this asymmetry. The parameter "intercept" has a covariance of 1.611, indicating the relationship between the intercept and another variable.

Rank correlation test for Funnel plot asymmetry: Kendall's τ is a statistical measure used to assess the correlation between two rankings. In this case, the value is 0.402. The associated P-value for the rank test is 0.014, which indicates the probability of obtaining the observed correlation by chance.

Regression test for Funnel plot asymmetry ("Egger's test"): Egger's test is a regression test used to detect funnel plot asymmetry, which can suggest publication bias. The value of z in this test is 4.228, which is used to assess the asymmetry in the funnel plot. The associated P-value for the regression test is<0.001, indicating the significance level of the test results.

Table 3: Parameter Covariance of efficacy of Phosphodiesterase-5 Inhibitors in male infertility for control group

Parameter Covariances	
	Intercept
Intercept	1.611

Table 4: Regression test for Funnel plot asymmetry ("Egger's test") for efficacy of Phosphodiesterase-5 Inhibitors in male infertility for control group.

Regression test for Funnel plot asymmetry ("Egger's test")		
	Z	P
Sei	4.228	< .001

Table 5: Rank correlation test for Funnel plot asymmetry for of efficacy of Phosphodiesterase-5 Inhibitors in male infertility for control group.

Rank correlation test for Funnel plot asymmetry		
	Kendall's τ	P
Rank test	0.402	0.014

Funnel Plot

Funnel Plot is a graph designed to check for the existence publication bias which commonly used in systematic review and Meta-analysis.in the absence of publication bias, it assumes that studies with high precision will be plotted near the average and studies with low precision will be spread evenly on both sides of the average, creating a roughly funnel-shaped

distribution. Deviation from this shape can indicate publication bias.

For control group, plot is not perfectly symmetrical and have clusters which indicate some degree of publication bias. Overall, this funnel plot suggests some publication bias.

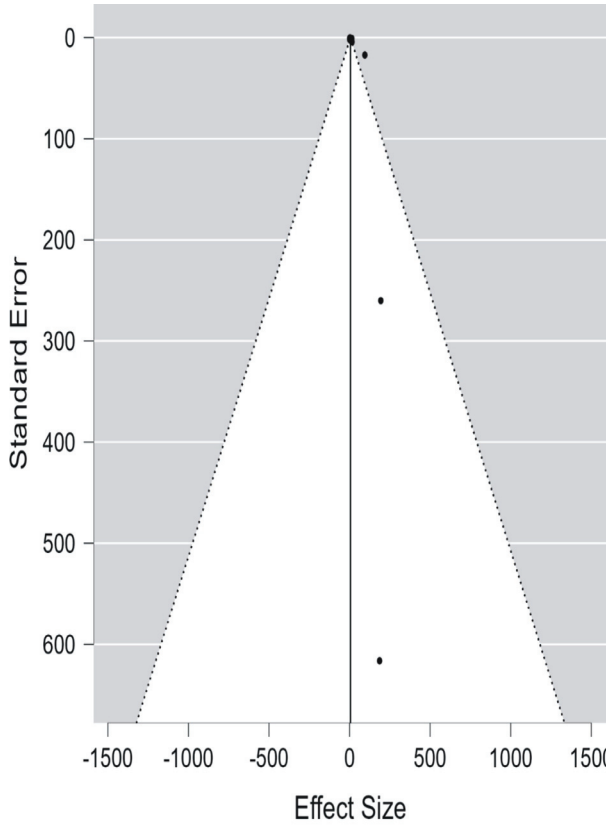


Fig. 1. Funnel Plot to investigate publication bias in Meta-analysis for the efficacy of Phosphodiesterase-5 Inhibitors in male infertility control group where study size is plotted against effect size.

Forest Plot

A forest plot is a visual representation of results of multiple studies that are part of a Meta-analysis. It is useful tool for summarizing information from individual studies.There are multiple studies represented by the horizontal lines and associated text. The effect sizes for these studies vary, with some showing positive effects and some showing negative effects.The standard errors for some studies are quite large, indicating low precision in the effect size estimates.The diamond suggests that the pooled effect size is not very precise.

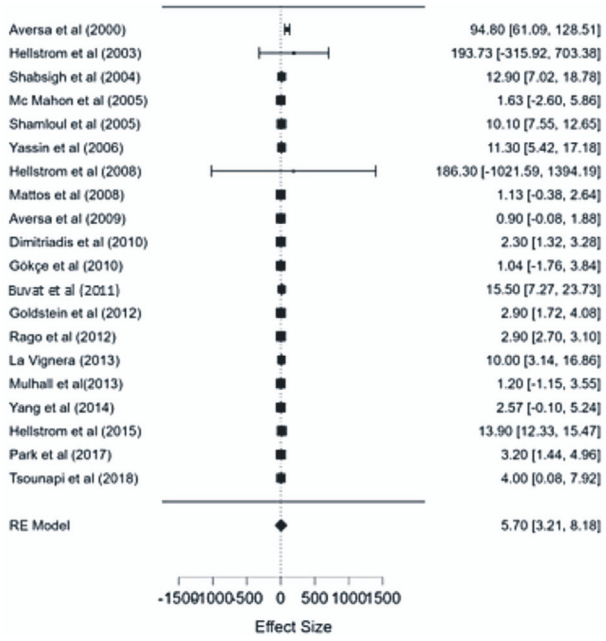


Fig. 2. Forest Plot for the graphical representation of the results from multiple studies on efficacy of Phosphodiesterase-5 Inhibitors in male infertility for control group, showing the size of the effect observed in each study.

For experimental group, the parameter "intercept" has a covariance of 5.084, indicating the relationship between the intercept and another variable.

Rank correlation test for Funnel plot asymmetry: In this case, the value is -0.016. The associated P-value for the rank test is 0.922, which indicates the probability of obtaining the observed correlation by chance.

Regression test for Funnel plot asymmetry ("Egger's test"): The value of z in this test is 3.137, which is used to assess the asymmetry in the funnel plot. The associated P-value for the regression test is 0.002, indicating the significance level of the test results.

Table 6: Regression test for Funnel plot asymmetry ("Egger's test") for for efficacy of Phosphodiesterase-5 Inhibitors in male infertility for experimental group.

Parameter Covariances	
	Intercept
Intercept	5.084

Table 7: Rank correlation test for Funnel plot asymmetry for efficacy of Phosphodiesterase-5 Inhibitors in male infertility for experimental group.

Rank correlation test for Funnel plot asymmetry		
	Kendall's τ	P
Rank test	-0.016	0.922

Table 8: Regression test for Funnel plot asymmetry ("Egger's test") for for efficacy of Phosphodiesterase-5 Inhibitors in male infertility for experimental group.

Regression test for Funnel plot asymmetry ("Egger's test")		
	Z	P
Sei	3.137	0.002

Funnel Plot

For experimental group funnel plot is asymmetrical and cluster shows, it means for experimental group, funnel plot suggests some publication bias.

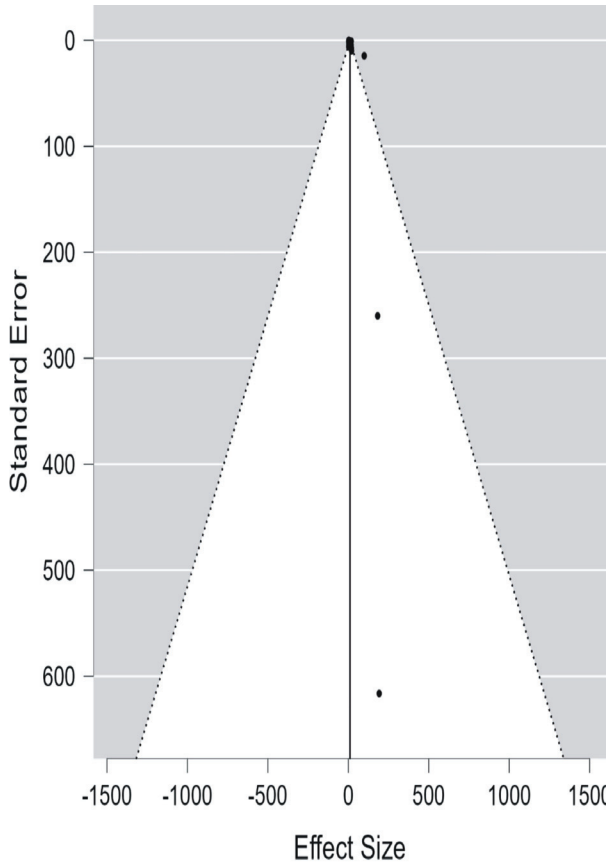


Fig. 3. Funnel Plot to investigate publication bias in Meta-analysis for the efficacy of Phosphodiesterase-5 Inhibitors in male infertility for experimental group where study size is plotted against effect size.

Forest Plot

For the experimental group, effect sizes for these studies vary, with some showing positive effects and some showing negative effects. The standard errors for some studies are quite large which indicates low precision in the effect size estimates. The diamond suggests that the pooled effect size is not very precise.

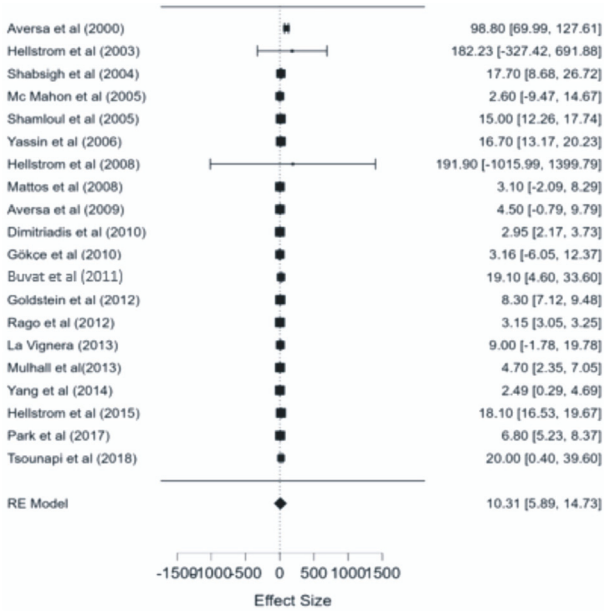


Fig. 4. Forest Plot for the graphical representation of the results from multiple studies on efficacy of Phosphodiesterase-5 Inhibitors in male infertility for experimental group, showing the size of the effect observed in each study.

ANOVA to analyze the variance in the meta-data and determine the significance of the regression model on efficacy of Phosphodiesterase-5 Inhibitors in reversal of male infertility for control and experimental groups

In ANOVA though "regression" and "residual" model was employed to analyze the variance in the meta-data and determine the level of significance. In regression section the sum of squares represented the total variability explained by the regression model, which were 48828.441 with 1 degree of freedom (df) for the regression. The mean square was calculated by dividing the sum of squares by the degrees of freedom, resulting in 48828.441. The F statistic tests the overall significance of the regression model, which were 51.661. The P-value indicated the significance level of the F statistic, which is less than 0.001 (highly significant).In case of residual section, the sum of squares represented the unexplained variability in the data after considering the regression model, which was 17013.028 with 18 degrees of freedom for the residual. The mean square was calculated by dividing the sum of squares by the degrees of freedom, resulting in 945.168. The total sum of squares was 65841.469 with a total of 19 degrees of freedom.

Table 9: ANOVA to analyze the variance in the meta-data and determine the significance of the regression model on efficacy of Phosphodiesterase-5 Inhibitors in male infertility for control group.

ANOVA (control group)						
Model		Sum of Squares	Df	Mean Square	F	P
2	Regression	48828.441	1	48828.441	51.661	< .001
	Residual	17013.028	18	945.168		
	Total	65841.469	19			

The intercept model is omitted, as no meaningful information can be shown.

For experimental group, in regression section the sum of square represented the total variability explained by the regression model, which is 47198.206 whereas, in residual section the sum of square represented the unexplained variability in the data after considering the regression model, which is 14933.224.The F-value showed statistic tests of overall significance of the regression model, which is 56.891. The p-value clearly indicated the significance level of the F statistic, which is less than .001. Thus, the result of ANOVA for experimental group showed that efficacy of Phosphodiesterase-5 Inhibitors produced significant effect *(F* = 0., $p > 0.001$) on the reversion of male infertility respect of Meta-analysis of various studies done by researchers.

Table 10: ANOVA to analyze the variance in the meta-data and determine the significance of the regression model on efficacy of Phosphodiesterase-5 Inhibitors in male infertility for experimental group.

ANOVA (experimental group)						
Model		Sum of Squares	Df	Mean Square	F	P
H_1	Regression	47198.206	1	47198.206	56.891	<.001
	Residual	14933.224	18	829.624		
	Total	62131.430	19			

The intercept model is omitted, as no meaningful information can be shown.

DISCUSSION

In present study a method called Meta-analysis was employed, which combines results from different studies to get a clearer picture of the effectiveness of drug Phosphodiesterase-5 Inhibitors used in the treatment of male infertility. The data presented includes various statistical measures that help researchers understand the results better. This study was based on comparison between two group i.e., control and experimental group. The control group does not receive the drug, allowing researchers to see what happens without treatment while experimental group receives Phosphodiesterase-5 Inhibitors therapies to understand the drug's effects (Puia *et al*., 2022). The fixed and random effect shows the significant effect and the test of residual heterogeneity indicates that there is significant residual heterogeneity among the studies included in the Meta-analysis. Funnel plotsare not perfectly symmetrical and have clusters thatshowsome publication bias and forest plots show less precision (Prendergast *et al*., 2002). The statistical tests used show that the results are reliable and that the drug has a meaningful effect compared to the control group. In summary, this research provides evidence that Phosphodiesterase-5 Inhibitors can significantly impact male infertility.

CONCLUSION

According to this systematic review and Meta-analysis, although treatment of Phosphodiesterase-5 Inhibitors during male infertility showed positive results by improving male fertility. This drug was used to treat male infertility especially for the treatment of erectile dysfunction. In conclusion it is suggested that further research is needed to validate the wide use of Phosphodiesterase-5 Inhibitors for male infertility treatment. Overall, drug Phosphodiesterase-5 Inhibitors could be a promising option for men struggling with erectile dysfunction, but it is important to consult with a doctor before any new treatment.

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