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Potential of Preoperative Testosterone Stimulation Therapy to Reduce Complication in Hypospadias Repair: A Systematic Review and Meta-Analysis

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Introduction. The pre-operative hormone stimulation is recommended for hypospadias patients, especially those with small penis, to improve the results and outcomes of hypospadias repair. We conducted a systematic review and meta-analysis to evaluate the effectiveness of pre-operative testosterone stimulations before hypospadias repair.
Methods. We performed a comprehensive search for relevant studies from PubMed, Medline, Cochrane, Proquest, and Embase from August 2000 until August 2023 . The phrases "hypospadias" and "testosterone treatment" were utilized. Only studies focusing on patients diagnosed with hypospadias were considered. This analysis exclusively included English-language papers, randomized control trials, cohort studies, and case-control studies. Case studies without comparable groups were excluded. Editorials, comments, and review articles were excluded from the study. We used the PRISMA guidelines for this systematic review and meta-analysis report. RevMan version 5.4.1 was used to analyze and evaluate the data.
Results. A total of 832 patients undergoing urethroplasty were evaluated in 7 studies. A total of 372 patients were categorized into the intervention group, which received testosterone hormone therapy (parenteral, intramuscular, and topical). Patients who receive preoperative testosterone therapy have a 0.68 reduced risk of complications rate compared to those who did not (P = 0.03, I2 = 28%, CI: 0.68, OR: 0.48 - 0.96), reduced meatal stenosis (P = 0.04, OR: 0.66, 95% CI: 0.44 - 0.98, I2 = 28), reduced the risk of postoperative glans dehiscence (P = 0.0004, OR: 0.46, 95% CI (0.30-0.71), I2 = 57%), and reduced risk of fistula urethrocutaneous (P = 0.03, OR: 0.58, 95% CI: 0.36 - 0.94, I2 = 22%).
Conclusion. Pre-operative testosterone stimulation can improve surgical outcomes. Complication rates, such as meatal stenosis, glans dehiscence, and fistula, showed a significant effect in patients who intervened with testosterone stimulation pre-hypospadias repair.

Keywords: hypospadia, improve, outcome, repair, testosterone

Introduction

Hypospadias is a congenital abnormality of the penis, with the position of the meatus and ventral curvature being the two main variables that determine the severity of hypospadias. The meatus location at the ventral of the penis is sometimes accompanied by ventral foreskin deficiency. The width of the urethral plate, the size of the glans, and the size of the penis may influence the choice of surgical technique, surgical success, and complications [1-2].

Hypospadias surgery is performed to help children urinate smoothly without spraying or straining. Hypospadias repair must also consider the complications and cosmetic appearance of the penis [3]. Therefore, this repair is a challenge for surgeons especially in men with small penis size. Many surgeons apply the use of temporary penis enlargement, which is done using hormonal therapy [4].

Pre-operative hormonal stimulation was first applied in 1971 and has been used as a preparation for hypospadias repair surgery to reduce complications. Hormonal therapy is often applied to patients with small glans and proximal meatal location to enlarge the size of the glans and penis temporarily. Hormonal therapy for patients with

hypospadias surgery also aims to improve vascularization of the preputium [5-6].

Some hormones commonly used as pre-operative hypospadias therapy are testosterone, dihydrotestosterone, and βHCG. Urologists must also choose between parenteral, intramuscular or topical intervention. Some studies have shown that pre-operative hormonal stimulation can prevent and even has no effect on the incidence complications [7-8].

Due to differences in opinion regarding preoperative hormonal stimulation in hypospadias patients, we conducted a systematic review and meta-analysis to evaluate the effect of pre-operative hormonal therapy on hypospadias postoperative complications.

Materials and Method

A protocol was pre-established to determine the analytical procedures and inclusion criterias for this study. The Population, Intervention, Control, Outcome, Study Design (PICOS) framework establishes the inclusion criteria for the literature search. Only studies focusing on patients diagnosed with hypospadias were considered. From August 2000 until August 2023, we conducted a thorough literature search across the following databases: PubMed, Medline, Embase, Cochrane, and Proquest, using the keywords hypospadias and testosterone treatment. We used the Preferred Reporting Items for Systematic Review and Meta-Analysis of Observational Studies in Epidemiology (PRISMA) guidelines for this systematic review and meta-analysis report. RevMan version 5.4.1 was used to analyze and evaluate the data.

This analysis exclusively included English-language papers, randomized control trials, cohort studies, and case-control studies, without any constraints on publication year. Case studies without comparable groups were excluded. Editorials, comments, and review articles were also excluded from this study. Non-peer-reviewed publications, such as vital statistics reports, dissertations, and similar documents, were excluded.

Surgical complications and adverse consequences are part of important considerations of surgery outcomes, including any reported deviation from the normal postoperative course. We conducted a statistical analysis where we assigned equal importance to each problem in the included study, and classified patients as either having a problem or not.

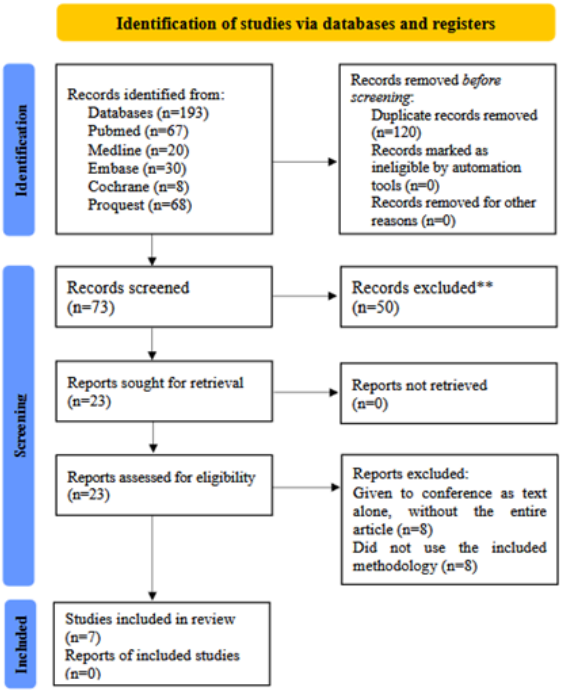

Figure 1. Flowchart diagram of systematic review

Result

A total of 193 potentially eligible articles were collected from the initial database search (Fig. 1). A total of 135 duplicated studies were excluded. Title and abstract screening led to the exclusion of 23 studies. Due to the study titles using different hormone therapies, 20 studies were excluded. A total of 8 studies were excluded because the studies described different outcomes and did not seek to compare. Therefore, a total of 7 studies were included in the final analysis and are outlined in Table 1.

In this study, a total of 832 patients underwent urethroplasty were evaluated in 7 studies. A total of 372 patients were categorized to the intervention group, which received testosterone hormone therapy (parenteral, intramuscular, and topical). The complication rate, such as meatal stenosis, glans dehiscence, and fistula, was measured.

Fig. 2 displays a forest plot of the complication rate in the selected studies. I2 values of 28% indicate that the studies have minimal heterogeneous data. We carried out the forest plot analysis using a fixed-effect model. With a 95% confidence interval of 0.48 to 0.96, the odd ratio is 0.68, and P= 0.03. In summary, a statistically significant difference exists in the complication rate between the intervention and control group. Patients who receive preoperative testosterone therapy have a 0.68 reduced risk of complications

Table 1. Characteristics of included studies

Authors	Study design	Penile Circumference (mm)		Glans Width (mm)		Hypospadia Classification (n) (%)			Age	Sample size (n)		Intervention	Dosage and schedule
		Before	After	Before	After	Distal	Proxi-mal	Peri-neal		Contr ol	Inter-vention		
Walid et al, 2022	Prospective study	7.22	7.33	17.78	18.40	39 (76.47)	12 (23.53)	-	< 12 month	36	15	Sustanon (testosterone esters of propionate, phenylpropionate, isocaproate and decanoate)	1/2 ampoule of 250 mg sustanon is given once a month for maximum 3 doses.
Abdallah et al, 2021	Retrospective study	6.8	7.9	12.1	17.2	104 (57.14)	78 (42.86)	-	6 month – 6 years	98	84	Topical testosterone (testosterone gel 1%)	Testosterone gel 1% was applied once daily over the ventral aspect of the penis for 3 weeks.
Wali et al, 2020	Prospective study	8.5	9.4	10.5	14.6	27 (67.5)	13 (32.5)	-	6 month – 3 years	20	20	Topical testosterone (testosterone gel 1%)	Study groups were treated by testosterone gel 1% for 30-40 days and stopped one month before surgery.
Babu et al, 2017	Prospective randomized study	22.5	22.8	17.5	21.8	186 (100)	0 (0)	-	< 9 month	92	94	Intramuscular Testosterone enanthate	Three doses enanthate 2 mg /kg is given at the age of 9,10, and 11 months.
Rynja et al, 2017	Retrospective study	91	105	25	27	90 (74.38)	31 (25.62)	-	Adult men operated for hypospadias in childhood	87	34	Testosterone treatment was either topical or intramuscular	5% sustanon topical cream twice a day during two periods of 14 days (separated by 1 week). Intramuscular therapy sustanon 25 mg per week for 2-3 weeks.
Chen et al, 2015	Randomized controlled trial	19.3	29.9	14.5	17.4	0	54	16	Children with primary microphallic hypospadias	36	34	Oral testosterone undecanoate	Testosterone groups were treated with 2 mg/kg/day of oral testosterone undecanoate with 120 mg/day maximum dose. Each treatment was 3 months.

compared to those who did not (P= 0.03, I2= 28%, OR= 0.68, CI= 0.48-0.96).

Fig. 3 shows a fixed-effect forest plot model of meatal stenosis. The investigations are low heterogenous data (I2 statistics of 28%). The data shows significant changes between the intervention and control group. There is a significant reduction (P= 0.03) in meatal stenosis complications among patients who underwent intervention, compared to the control patients (OR= 0.66, 95% CI= 0.44-0.98).

Fig. 4 shows a significant difference between the intervention and control groups in case of postoperative glans dehiscence risk. The forest plot below demonstrates that preoperative testosterone intervention significantly reduced the risk of postoperative glans dehiscence in pediatric patients with hypospadias by 0.46 compared to control individuals (P= 0.0004, OR= 0.46, 95% CI (0.30-0.71)), with moderate data heterogeneity (I2= 57%).

Fig. 5 illustrates the fixed-effect model forest plot of the fistula from the included studies. An I2 score of 22% indicates that the studies are of low heterogeneity. The odd ratio stands at 0.58, with the 95% confidence range extending from 0.36 to 0.94. There is a substantial disparity in fistula formation between the intervention and control group.

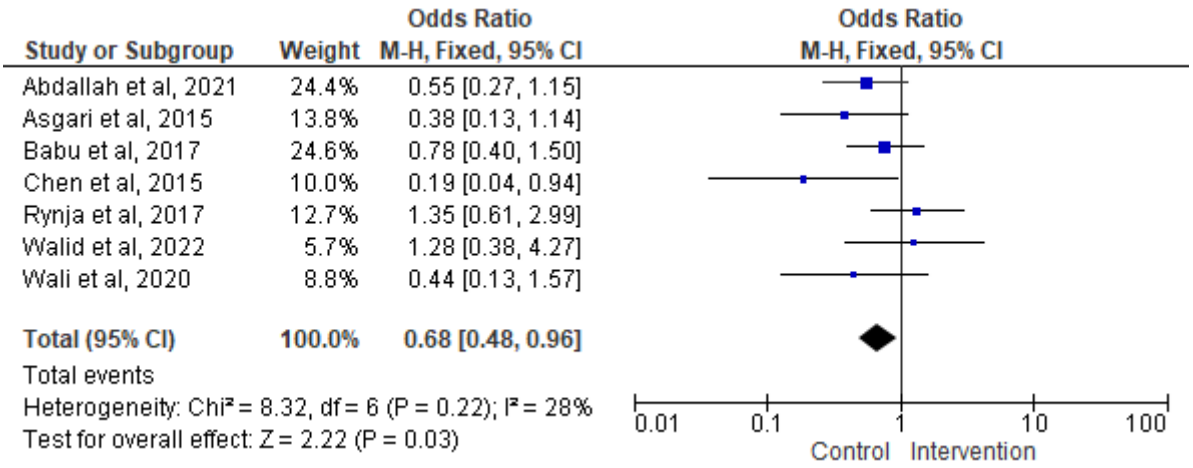

Figure 2. Forest plot of the complication rate in the included studies

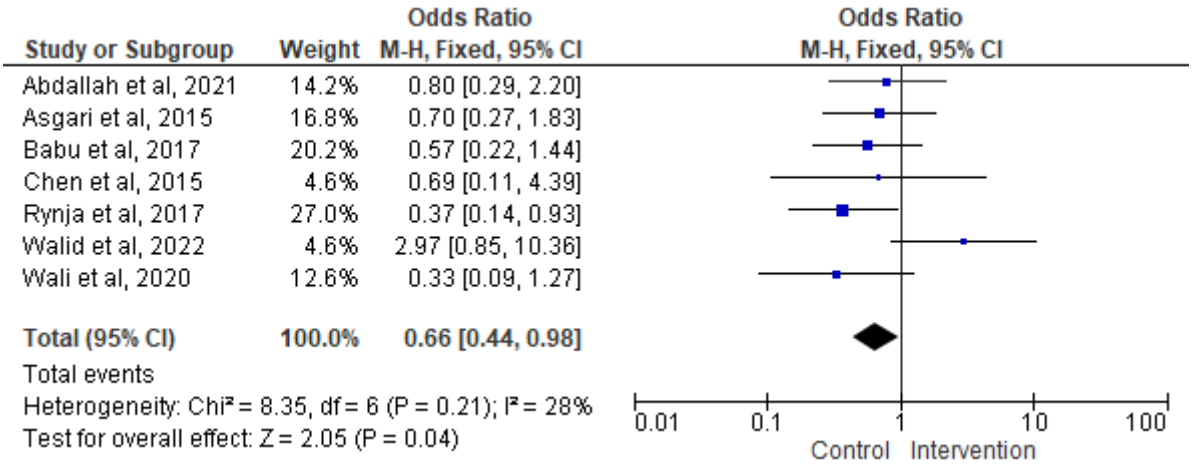

Figure 3. Forest plot of the rate of meatal stenosis in the included studies

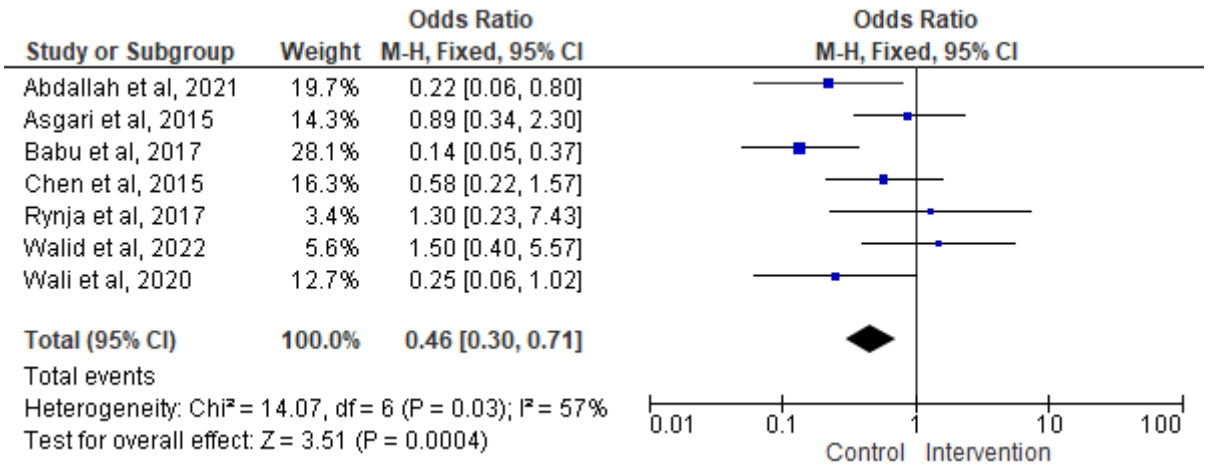

Figure 4. Forest plot of the rate of glans dehiscence in the included studies

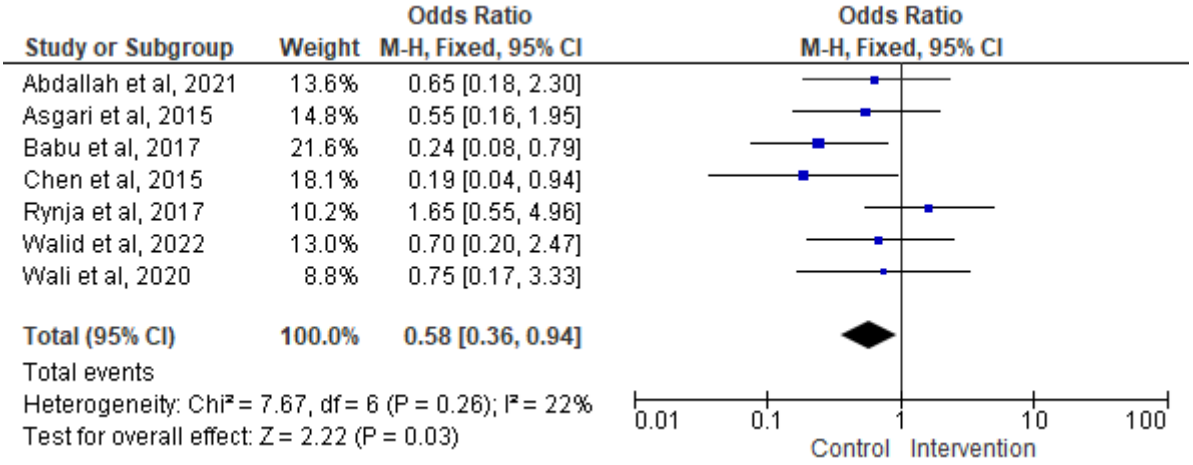

Figure 5. Forest plot of the rate of Fistula in the included studies

Discussion

The exact cause of hypospadias is still unknown, but the disruption of the testosterone biosynthesis pathway is one of the factors. Hypospadias surgery is usually recommended at an early age. The size of the penis, penile length, glans width, or tissue structure around the penis, is taken into consideration by the surgeon before performing surgery. Post-operative complication of hypospadias might mostly be caused by surgery difficulties due to the penis sizes. Therefore, several studies have conducted several methods to increase the size of the penis. Thus, helping surgeons to get perfect surgical results without postoperative complications [9–11].

Proximal hypospadias is closely associated with complications such as urethrocutaneous fistulas and dehiscences, up to 70%. Therefore, surgeons need to consider the next surgical technique to perform. The choice of surgical procedure and the skill of the surgeon are some of the important factors that can affect the outcome of hypospadias repair [12-13].

Reconstruction of hypospadias is a challenging repair surgery. The quality of penile tissue is a factor that must be considered before performing surgery. Better functional outcomes, good cosmetic results and lower postoperative complications are the principal goals of hypospadias repair. Therefore, the use of preoperative hormone stimulation is expected to increase the foreskin, penile length, glans circumference, and neovascularity of the tissues, which are expected to reduce postoperative complications [11,13].

The use of hormones such as testosterone and dihydrotestosterone or human chorionic gonadotropin is expected to stimulate the development of glans and penis size, as well as the availability of tissue for good surgical correction.

Testosterone is the most commonly used hormone as a therapeutic hormone before hypospadias surgery [9,14].

The pre-operative hormone stimulation before hypospadias repair in some studies is recommended in patients with small penis that can improve the results and outcomes [16]. Ali et al. found that after administration of intramuscular testosterone for 3 months (2 mg/kg/dose), significant results were obtained. In the study, there was an increase in SPL (stretched penile length), penile circumference at base and glans width which provided ease of operation. And there was also a significant difference in microvessel density in the intervened group compared to the control group [9].

Pre-operative hormonal therapy for hypospadias is still a matter of debate. The role of pre-operative testosterone in hypospadias repair is not fully established and there are few well-designed studies to prove its efficacy in hypospadias repair [3]. Walid et al. showed complications after testosterone administration and did not prove any benefit after the administration of testosterone stimulation in patients with distal and mid-shaft hypospadias. However, the difference in results between the intervention and control group was not significant. Wali et al. [17] also studied that preoperative testosterone using testosterone topical gel 1% stimulation does not have a significant effect on the post-operative complication and cosmesis outcomes.

On the other hand, some comparative studies have shown that pre-operative testosterone results in the low incidence of complications and significant increases in penile length and glans circumference, induction of neovascularization and decreasing complication rates. Khokar et al. studied 45 patients with proximal and mid-penile hypospadias with intramuscular testosterone administration. A total of 40 patients showed a response to hormone therapy, 23 patients showed a significant increase in phallic size and 17 responded although not significant [18]. Abdallah et al. [19] also used topical testosterone on patients whose ages range from 6 months to 6 years old. Their study showed an improvement in surgery outcomes in patients with topical testosterone administration than the control group.

Conclusion

Testosterone administration can reduce the postoperative complication rate in hypospadias patients. Complication rates, such as meatal stenosis, glans dehiscence and fistula showed a significant effect in patients who intervened with testosterone stimulation.

Author Contributions

AM and FAM were responsible for collecting relevant literature, reviewing each literature, and preparing the initial research manuscript. AM and AP were responsible for extracting the data and structuring the research results, discussion, and conclusion.

Conflict of interest

The authors declare no conflict of interest.

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