



PREOPERATIVE HORMONAL THERAPY WITH TOPICAL AND INTRAMUSCULAR TESTOSTERONE IN HYPOSPADIAS: ASYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Hypospadias reconstruction is an operation associated with numerous complications, namely: bleeding, edema, hematoma, wound infection, and scar formation. Hormonal therapy is shown as additional strategies to obtain a better intraoperative outcome. However, no meta-analysis that investigates the efficacy and adverse events of preoperative hormonal treatment with topical and intramuscular testosterone in hypospadias.

Methods: This study performed literature study in Medline, Science Direct, and Cochrane Library through August 2018 without year restriction, only English journals were included with a hand search using Selected Reporting Items for Systematic Reviews and Meta-analysis of Observational Studies in Epidemiology Guidelines.

Results: Five studies were included in this meta-analysis. Among these studies, two were randomized clinical trial multi-center studies. Two studies were prospective studies with various length of median follow-up. One study was retrospective. The total patients included in this study was 585. The outcomes of this study were complications rate after receive any testosterone treatment and the group that did not receive any intervention before surgery. In addition, the complication namely meatal stenosis, fistula, glans dehiscence, scarring, reoperation rate, urethral diverticulum, fine pubic hair, and sexual precocity. The only significant difference between the intervention and control group was glans dehiscence (OR 0.40 with the 95% CI of 0.17 until 0.97).

Conclusions: In this study, we found significantly lower complication rate for glandular dehiscence. On the other side, reoperation rate, urethral-cutaneous fistula, meatal stenosis, and penile scarring in hypospadias children showed no significant difference outcome or side effects in the route of administration (whether parenteral or topical) in receiving testosterone treatment group compared to the control group.

KEYWORDS : hypospadias, testosterone

INTRODUCTION

Hypospadias is a congenital penile abnormality that is defined as an abnormal location of the urethral meatus on the proximal ventral penis and sometimes presented a ventral foreskin deficiency and ventral penile curvature.^{1,2} In the reconstruction of hypospadias there found various complication such as bleeding, hematoma, edema, wound dehiscence, wound infection, skin and flap necrosis, penile erection, penile torsion, meatal stenosis, urethral strictures, urethral diverticula, urethro-cutaneous fistulation, and scar formation.^{2,3}

Preoperative hormonal therapy was proposed to improve the surgical outcome of those who repair hypospadias. The hormones are Human Chorionic Gonadotropin (HCG), Dihydrotestosterone (DHT), or Testosterone (T).^{2,3} A better intraoperative conditions is indicated while using hormonal therapy before surgical therapy.^{1,2,4} The use of preoperative androgen will increase vascularization of the prepuce; this condition will allow for a decrease in fibrous tissue formation and inflammation. In postoperative condition, the effects of hormonal therapy are the decreasing of complication and the growth of cutaneous nutrition, and oxygenation which improve scar formation.^{2,3} Testosterone was known to successfully increase the width of the glans by mean of 4.5mm in proximal hypospadias babies with small glans, which will be reducing complications associated with small glans size.^{1,2,5} However, in some literature, we had to disagree on potential adverse effects of preoperative hormonal therapy like increase of erections, pubic hair growth, accelerated linear height, and bone age.^{2,3,6} The androgen was considered to inhibit wound healing and increase inflammation. Recent prospective, some non-randomized studies suggested that treating pediatric hypospadias patients with hormone stimulation might increase the risk of complications.^{2,7} Further, a review of a cohort of patients undergoing treatment for hypospadias, like 49% (19 patients) presented evidence-based of relative androgen resistance.² The hormonal therapy preceding hypospadias correction is a

controversial subject for there is limited data in the literature to support such a practice. It is because of the risks of postoperative complications.^{1,2} Furthermore, there are considerable variabilities in clinical practice about choices of hormonal therapy, topical or parenteral usage, time of use, and a dose of treatment.^{1,4,6} Therefore, we hypothesized that Preoperative Hormonal Therapy (PHT) with testosterone would not improve postoperative complications in hypospadias patients. Our meta-analysis evaluated and analyzed different individual studies and assessed the prevalence of postoperative complications in hypospadias pediatric patients treated with preoperative topical and intramuscular testosterone. We aim to provide accurate information about whether PHT with testosterone in hypospadias repair is sufficient to determine the complications from a testosterone use group and the group of not receive any intervention.

METHODS

This study included randomized control trials, cohort, and case-control studies without year restriction, but only English-language-mode studies were included. Case series which lack in comparator groups, were excluded. Other publications, including editorials, commentaries, and articles review were excluded. The paper that not subjected to peer review (i.e., reports of data from vital statistics and dissertations or these) were also excluded. When there was a publication that results as duplication from our search strategy, our analyses only selected one study based on a hierarchical assessment of the comparability of study groups, the period of study (preference for more recent), and the number of patients (Supplementary data) to prevent duplication.

Types Of Participants And Exposure

This study reviewed the studies that reported boys diagnosed with hypospadias as a primary diagnosis, exposed to some form of hormonal stimulation preoperatively or post-operatively, underwent surgical repair, reporting of postoperative complications, and clinical research designation. All study

types were included in the review.

Outcome Measures

The primary outcome are the complications and side effects after surgery. They were defined as any documented deviation from the ordinary postoperative course according to the original studies included. All complications were given equal weight in our statistical analysis, and patients were categorized as having a complication or not, based on information stated in each report. The complication will be analyzed by comparing the groups that give androgen before surgery with the control that not receive any intervention.

Data Searching And Literature Screening

This study specified the methods of the analysis and inclusion criteria in an advanced protocol. The inclusion criteria are defined by the literature search using the PICOS (Population, Intervention, Control, Outcome, Study design) approach. Only studies reporting on boys diagnosed with hypospadias as a primary diagnosis. These studies were conducted with a systematic literature search in August 2018, in the following databases: Medline, Cochrane CENTRAL, and Science Direct. The combination of the term "Testosterone Therapy and Hypospadias" was used in this study. The Reporting Items for Systematic Review and Meta-Analysis of Observational Studies in Epidemiology (PRISMA) guidelines for reporting of this systematic review and meta-analysis were used in this study. The Reporting Items for Systematic Review and Meta-Analysis of Observational Studies in Epidemiology (PRISMA) guidelines can be seen in Figure 1.

Eligibility Criteria

This study is a systematic review and a meta-analysis study. The data was conducted by patient, intervention, comparison, and outcome. The data searching process was not limited by publication date and only full-text articles in English were included

Statistical Analysis

Data analysis was conducted by two independent reviewers. Studies were assessed based on the Oxford Center of Evidence-Based Medicine and analyzed using Review Manager 5.3 for the data meta-analysis. Weighted mean differences and odds ratios were used to analyze the variables of each study. The Confidence Interval (CI) was 95%, and a p-value of less than 0.05 was considered significant.

Cochrane Q test was performed to assess the heterogeneity of the studies. Heterogeneity was evaluated using I² statistics; a value less than 50% indicated homogenous studies, and a fixed-effects model was used. If the value was more than 50%, studies were considered heterogeneous, and a random-effects model was used.

RESULTS

Literature Search Results

The initial search yielded 112 potential literature citations, including 32 records from Pubmed, two from Cochrane Library, 26 from EMBASE, and 52 from ISI Web of Science. Seventy-eight studies were excluded because they were duplicates. According to the predetermined selection criteria, ten potentially relevant studies were selected and retrieved for a full-text assessment after exclusion at the title and the abstract stages. Of the remaining ten articles, one was duplicate, one was editorial, one study used additional therapy, and three others were not aim to compare and to duplicate. Finally, a total of five studies were deemed eligible for inclusion in this review.

Study Characteristics

Table 1 depicts the study characteristics and methodology of

the five studies included in the meta-analysis. Among these studies, two were randomized clinical trial multi-center studies.¹⁻⁵ Two studies were prospective study with various length of median follow up.⁶⁻¹⁰ One study was retrospective. There were 585 patients involved in the study. The characteristics of the included studies can be seen in Table 1.

Measurement Of Outcome

We included the studies in which hypospadias was measured using any of the existing and validated instruments. In the study, there are three studies that patients received a daily application of testosterone (parenteral, intramuscular, intradermal) with follow up variations compared to control groups, and two studies received a regular use of testosterone (parenteral, intramuscular and topical) with various follow-up methods. The outcomes measured were complication rate after treatment, such as meatal stenosis, fistula, glans dehiscence, scarring, reoperation rate, urethral diverticulum, fine pubic hair, and sexual precocity. The complications rate can be seen in Table 2.

Meta- Analysis Results

Figure 2 illustrates the forest plot of the complication rate in the included studies. The studies are homogenous, which are indicated by I² statistics of 14%. The analysis is performed using a fixed-effect model in this forest plot. The odds ratio is 0.80, with the 95% Confidence Interval of 0.52 until 1.25. As conclusion, there is no significant difference between the experimental group and the control group towards the complication rate.

The forest plot in Figure 3 explains about meatal stenosis. The studies are homogenous (I² statistics of 10 %), which is performed using a fixed-effect model in a forest plot. This forest plot suggests no significant differences between cases and control groups. It shows from the odds ratio is 0.8, with the confidence interval of 0.33 until 1.96.

Figure 4 only shows significant difference in this study between the experimental group and the control group. These homogenous studies had a result about glans dehiscence statistically significant after giving DHT treatment compare to groups that no intervention before surgery. The odds ratio is 0.40, with the 95% Confidence Interval of 0.17 until 0.97.

Figure 5 depicts the forest plot of fistula in the included studies. The studies are homogenous, which are indicated by I² statistics of 0%. The analysis was performed a fixed-effect model in this forest plot. The odds ratio is 0.59, with the 95% Confidence Interval of 0.27 until 1.27. To conclude, there is no significant difference between the experimental group and the control group towards fistula formation.

The forest plot in Figure 6 is about the reoperation rate. The studies are homogenous (I² statistics of 10 %), which performed by using a fixed-effect model in the forest plot. This forest plot suggests no significant differences between cases and control groups. It shows from the odds ratio is 0.29, with the confidence interval of 0.05 until 1.67. Regarding the same result about complication, in Figure 7, we find no significant difference in this study between the experimental group and the control group.

DISCUSSION

Hypospadias is one of the most common male genitalia malformations. The incidence of hypospadias is increasing over time.⁸ The surgery for hypospadias aims to reconstruct the urethra to the tip of the glans and to achieve an excellent cosmetic result. The complications from the surgery included glans dehiscence, urethro-cutaneous fistula, meatal stenosis, and penile scarring. In decades, using hormonal stimulation before the operation has been practiced.⁹ Testosterone has

been used for further investigations. Nonetheless, the use of testosterone remains controversial. To date, there is no standard protocol that has been established.

Androgen stimulation is provided to improve the surgical results. It is postulated that androgen stimulation promotes phallic growth, which will perform the easier surgical correction.¹⁰ Moreover, Androgen stimulation resulted in fewer complications. Previous studies showed that the use of androgen stimulation (testosterone, dihydrotestosterone and human chorionic gonadotropin) increased penile length, glans circumference, and tissue vascularity.¹¹

Hypospadias surgery is a complex surgery and involves several variables, likely anatomical variations, tissue handling, surgical technique, suture material, and stenting. The studies reported that the patients underwent different surgical repair techniques, such as OIF, TIP, Koyanagi urethroplasty, 2-stage repair, and buccal mucosa graft repair.¹²

Androgen stimulation has been thought to improve surgical results.¹² However, a pooled analysis showed a possible relationship between hormonal use and increased complication rates in patients with severe hypospadias. Meanwhile, selection results were bias. The bias may happen due to selected patients exposed to hormonal treatment included those with some of the most severe anatomical defects and unfavorable tissue characteristics.¹²

A study conducted by Kaya C, et al randomized 75 children with primary hypospadias who received a daily application of 2.5% DHT (3 months) before surgery or those who underwent TIP hypospadias repair without pretreatment. The study reported that the DHT group experienced a significantly lower complication rate (glandular dehiscence, fistulas) and reoperation compared to a control one. There were fewer reoperations for fistulas (1 vs. 4, $P > 0.05$), glandular dehiscence (0 vs. 3, $P < 0.05$) and meatal stenosis (0 vs. 2, $P > 0.05$) performed in patients who underwent DHT treatment than patients without treatment.¹³

The study also showed that DHT pre-treatment improved the penile cosmesis (moderate-to-severe scarring in 2 patients in the treatment group vs. 16 patients in the no-treatment group). For the cosmesis assessment, the critical parameter is scar formation after hypospadias repair. It was found to be significantly lower in children receiving DHT treatment compared to the control group. This parameter is thought to be important due to the proven importance of psychosocial satisfaction and the development of self-esteem in later periods of life. The study suggested that pretreatment with DHT transdermal gel is beneficial in declining complication and reoperation rates, as well as improving cosmetic results after hypospadias repair.¹³

Gorduz¹⁴ et al. gave monthly intramuscular injections and stopped when the penile length was at or above 35 mm. The study showed that patients who received the treatment less than three months before undergoing surgery presented with a much higher complication rate (50% fistula rate) than those treated more than three months before surgery (26.3%, $P > 0.34$). In addition to the hormonal treatment itself, the timing of the treatment and the timing between hormonal stimulation and the operation may have influenced surgical outcomes. So, the results of this study certainly cannot be used as a reference for comparison or indication for treatment.¹⁴

The study conducted by Babu¹⁵ et al. revealed that preoperative testosterone significantly increased the glans width, thereby reducing the complication and requirement for reoperation. It also improved cosmetic outcomes and parental

satisfaction. The total complications were significantly less in group 2b (17.9%) than in group 2a (50%). The reoperation rate (excluding the ones with minor glans dehiscence managed conservatively or meatal stenosis managed without patient dilatation) was significantly less in group 2b (11.5%) than in group 1 (23.1%).¹⁵

Studies have not demonstrated a significant differences in penile length revealed a higher occurrence of the pigmentation of the genitals, pubic hair growth, and skin irritation at the site of the application associated with topical use, suggesting that intramuscular hormone therapy is preferable to topical therapy.¹⁶

Topical medications are not absorbed through the gastrointestinal system, so they do not pass hepatic metabolism and associated with minimal side effects.¹⁷ On the other hand, the parenteral injection of hormones might limit parental compliance, particularly when the hormone is not suggested. It was reported that a bad early experience with injections might result in anxiety, which can make the next injection experience worse in children. In 3-months period, the secondary effects of transdermal DHT gel were minimal. Several complaints of irritating symptoms on the penile skin were reported in some children. One-third of patients reported to have erythema and temporary pruritus, also a darkening of the penile skin, but the darkening skin disappeared after treatment stop.¹⁶

In the case of intraoperative and postoperative complications, the data in the literature is not homogeneous regarding the description of complications. The studies that subjectively reported the absence of intraoperative complications have mainly referred to the absence of bleeding that was difficult to control.¹⁸ In this study, we found a significantly lower complication of glandular dehiscence in the treatment group than the control. On the other hand, the reoperation rate, urethro-cutaneous fistula, meatal stenosis, and penile scarring in children with hypospadias showed that there was no significant difference between the treatment group and the control.

CONCLUSION

Androgen stimulation resulted in fewer complications but not significant except glandular dehiscence. There was a significantly lower complication rate only for glandular dehiscence. On the other hand, the reoperation rate, urethro-cutaneous fistula, meatal stenosis, and penile scarring in children with hypospadias showed that there was no significant difference between the treatment group and the control.

List Of Abbreviations

HCG	= Human Chorionic Gonadotropin
DHT	= Dihydrotestosterone
T	= Testosterone
PHT	= Preoperative Hormonal Therapy (PHT)
PICOS	= Population, Intervention, Control, Outcome, Study design
PRISMA	= Preferred Reporting Items for Systematic Review and Meta-Analysis of Observational Studies in Epidemiology

Conflicts Of Interest

There are no conflicts of interest in the form of financial and personal relationships in the making of this research. Authors had access to all the study and no sponsors did intervene the data or the work.

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Tables And Figures

Table I. Characteristics Of The Included Studies

Author(s)	Publication Year	Study Design	Sample Size		Population	Mean age	Intervention	Exclusion Criteria	Follow up	
			Study group	Controls						
Rynja et al.	2017	Retrospective study	34	87	Adult men operated for hypospadias in childhood	N/A	Topical cream 5% twice a day during two periods of 14 days (separated by 1 week). Intramuscular therapy: 25 m Sustanon per week for 2-3 weeks.	Incorrect contact details, patients referred for redo hypospadias repair	N/A	
Babu et al.	2018	Prospective study	94	92	Patients with distal hypospadias	15.3 (1.0) months and 13.4 (1.1) months	Study group: three doses of intramuscular testosterone enanthate 2 mg/kg at the age of 9, 10, and 11 months. Controls did not receive any intervention	N/A	Over 4 years	
Asgari et al.	2015	Randomized controlled trial	91	91	Children with primary distal and mid-shaft hypospadias who underwent surgical repair	30 months	Study group: 2 mg/kg intramuscular testosterone enanthate once per month for 2 months pre-operatively	Previous history of hypospadias repair, any proven endocrine disorder	3 months	
Nerli et al.	2008	Prospective	10	11	Children with micro phallic hypospadias	N/A	Topical vs parenteral testosterone prior to surgery	Not stated	1 year	
Kaya et al.	2007	Randomized controlled trial	37	38	Children with primary hypospadias	33.4 ± 3.7	Study group: application of 2.5% DHT transdermal gel directly onto the penile shaft and glans once daily before bedtime for 3 months. DHT gel: 0.2 to 0.3 mg/kg body weight. Controls did not receive treatment	Children with endocrinological or clinical evidence of hypopituitarism and children with a history of hypospadias surgery	1- year follow up	

N/a = not applicable

Table II. Complications That Occurred

Author(s)	Publication Year	Complications	Meatal stenosis	Fistula	Glans dehiscence	Scarring	Reoperation rate	Urethral diverticulum	Fine pubic hair	Sexual precocity										
										Study group	Controls	Study group	Controls	Study group	Controls	Study group	Controls	Study group	Controls	Study group
Rynja et al.	2017	17/34	37/87	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Babu et al.	2018	22/94	26/92	8/94	6/92	6/94	7/92	7/94	13/92	N/A	N/A	14/94	22/92	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Asgari et al.	2015	5/91	12/91	1/91	3/91	4/91	7/91	0/91	1/91	N/A	N/A	N/A	N/A	0/91	1/91	N/A	N/A	N/A	N/A	
Nerli et al.	2008	2/10	3/11	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2/10	3/11	0/10	0/11	
Kaya et al.	2007	N/A	0/37	2/38	1/37	4/38	0/37	3/38	2/37	16/38	1/37	9/38	N/A	N/A	N/A	N/A	N/A	N/A		

N/a = not applicable

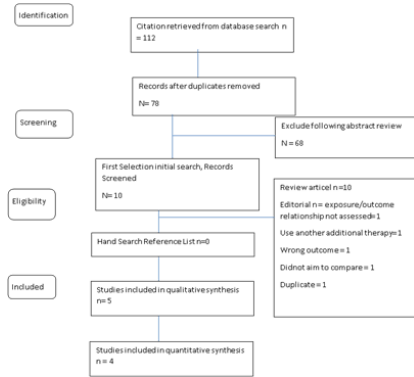


Fig 1. Preferred Reporting Items For Systematic Review And Meta-analysis Of Observational Studies In Epidemiology (prisma) Guidelines

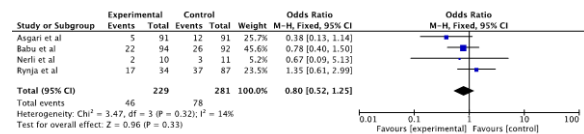


Fig 2. Forest Plot Of The Complication Rate In The Included Studies

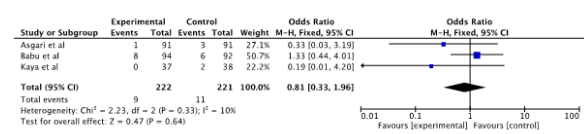


Fig 3. Forest Plot Of The Rate Of Meatal Stenosis In The Included Studies

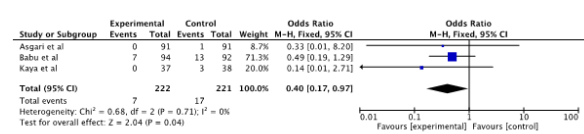


Fig 4. Forest Plot Of The Rate Of Glans Dehiscence In The Included Studies

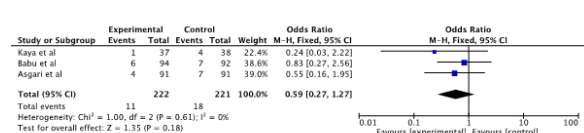


Fig 5. Forest Plot Of The Rate Of Fistula In The Included Studies

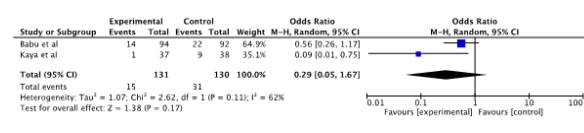


Fig 6. Forest Plot Of Reoperation Rate In The Included Studies

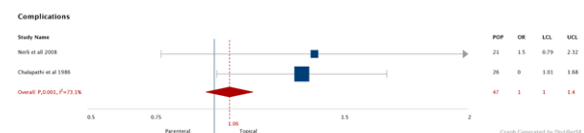


Fig 7. Forest Plot Of Complication Of Testosterone Administration

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