

Review Article

PRE-OPERATIVE HORMONAL ADMINISTRATION IN HYPOSPADIAS PATIENTS UNDERGOING URETHROPLASTY

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ABSTRACT

The gold standard of treatment for hypospadias patients is reconstructive surgery. The result and post-operative complication of urethroplasty were affected by glans diameter and penile length. Pre-operative testosterone administration, both parenterally or topically, has become one of the main interests to increase the size and diameter of penis to minimize post-operative complications. However, there has not been enough evidence to justify this recommendation. Therefore, we aimed to perform a systematic review and meta-analysis to evaluate the role of pre-operative testosterone to prevent postoperative complications after urethroplasty in hypospadias patients. Online databases of Medline, Scopus and Embase were searched until October 2021 to identify RCT studies evaluating the effect of testosterone hormone therapy in reducing post-operative complication on hypospadias patient undergoing urethroplasty. Data analysis was performed using RevMan 5.4. A total of 4 RCTs were included in the analysis of this study with the total of 211 patients. Pre-operative testosterone hormonal therapy significantly reduced the overall complications group (OR=0.17; 95% CI=0.04, 0.77; p=0.02), post-operative urethrocutaneous fistula (OR=0.4, 95% CI=0.19, 0.83, p=0.01). Finally, there was no significant effect on the incidence of dehiscence and meatal stenosis with OR of 0.59, 95% CI=0.23, 1.54, p = 0.28, and 0.277; 95% CI=0.04, 1.65; p=0.16, respectively. Pre-operative testosterone hormonal therapy could reduce overall complication and urethrocutaneous fistula in hypospadias patients undergoing urethroplasty.

Keywords: Urethroplasty; hypospadias; hormonal therapy; health risk

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1. The gold standard therapy of hypospadias is reconstructive surgery.
2. Glans diameter and penile length are factors influencing urethroplasty outcomes.
3. Many studies are being conducted to investigate various methods of increasing the size and diameter of the penis prior to the operation in order to reduce complications.
4. Preoperative testosterone hormonal therapy is able to reduce overall complication and urethrocutaneous fistula in hypospadias patient undergoing urethroplasty.

INTRODUCTION

Hypospadias is a congenital anomaly represented by an abnormal location of the urethra, which is located ventrally. The position may be located in the shaft, glans, scrotum, or perineum. It is one of the most common congenital anomalies in the field of Urology, with an incidence rate of 0.3 to 0.7% per birth (Yu et al. 2019). A large-scale national population survey in The United States of America (USA) showed that there

was an increase in hypospadias prevalence from 0.2% to 0.4% between 1970 and 1993 (Springer et al. 2016). The gold standard of treatment for hypospadias patients is reconstructive surgery to form a penis with an external urethral meatus located as close as possible to the tip of penis. The penis must also be able to erect in a straight position, resembling a normal circumcised penis as close as possible (Costa et al. 2021).

Hypospadias patients are recommended to undergo an operation before the age of 18 months, because a person would have already recognized his genital organs at that age (Kaya & Radmayr 2014). The ideal timing for surgery is between the ages of 6 and 12 months to reduce psychological stress and anxiety due to an invasive procedure (Perlmutter et al. 2006). With the improvement of perioperative care for *infantas* and instrumentation technology, the age of recommendation for reconstructive surgery continues to decrease. Several surgeons even suggested an intervention between the age of 4 to 6 months with excellent outcomes. The diameter of glans and penile length are independent factors affecting urethroplasty results. Mature glans will ease the technical aspect of repair procedure, resulting in fewer postoperative complications (Bahadir et al. 2016).

Age and microphallus as a comorbid are the main factors causing difficulties during the procedure due to a small surgical field. Therefore, many studies are investigating various methods to increase the size and diameter of the penis before the operation to reduce complications. Preoperative testosterone and other hormonal therapies administration, both parenterally or topically, has become one of the main interests of research due to its impact on the complication reduction (Krishnan et al. 2016). Several urologists have already recommended this method in patients with a small penis. Larger penis size is beneficial to allow for easier correction with a lower risk of complications (Kaya et al. 2008). However, as of the writing of this study, there has not been enough evidence to justify this recommendation.

We aimed to perform a systematic review and meta-analysis to evaluate the role of pre-operative hormonal therapy, including testosterone and its derivatives to prevent post-operative complications after urethroplasty in hypospadias patients.

MATERIALS AND METHODS

Study eligibility

The framework of PICOS which consisted of population (P), intervention (I), comparator (C), and outcome (O) was used in the framework of this study. Individual studies to be included in this meta-analysis must meet several criteria which the studies must be randomized controlled trials, the subjects were hypospadias patient undergoing urethroplasty with or without pre-operative testosterone, and the study has to contain 2 arms or more. The studies were excluded if it was case report, conference abstract, reviews, letters, or observational studies.

Search strategy and selection of studies

This study was a systematic review and meta-analysis. The subjects were pediatric patients with hypospadias. Comprehensive literature search was conducted from several databases including MEDLINE, EMBASE, and Scopus. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guideline was implemented in this study. Several keywords used in study included hypospadias, hypospadias repair, urethroplasty, testosterone, hormonal therapy, and hormone. The search was limited to human and male. The studies which were published until October 2021 were included. There were two independent reviewers who screened the study. Any contradictory and disagreement were resolved with the involvement of the third reviewers.

Data collection and risk of bias assessment

Extraction of data was conducted by the reviewers. The data were extracted into demographic data, study design, age, type of surgery, intervention protocol, serum testosterone, penile length, penile circumference, glans width, and time to procedure. Several outcomes that were evaluated were extracted into overall complication, *urethrocutaneous* fistula, wound dehiscence, and meatal stenosis incidence. The evaluation of risk of bias was also performed. For the assessment of RCTs, the Cochrane RoB2 tool was used.

Statistical analysis

The current meta-analysis was using RevMan 5.4 (Cochrane Collaboration, Oxford, UK). The studies included in this meta-analysis was only RCTs. Odds Ratios (OR) with 95% Confidence Interval was used to pool the estimation of the outcome. Mantel-Haenszel fixed-effects model was used to combine the trials if heterogeneity was low or less than 50% while Mantel-Haenszel random-effects model was selected if the heterogeneity test between studies was low or more than 50%. Statistical heterogeneity was assessed using I^2 test. The classification of I^2 test were 25%, 50%, and 75% which showed the inconsistency in low, moderate and high levels, respectively.

RESULTS

Comprehensive literature search was performed in several databases including Medline, Scopus and Embase using the search strategy. There were 311 articles identified. Through manual duplication exclusion process and using Mendeley software, 88

duplicated articles were removed. Afterwards, screening process was performed in 223 studies with title and abstract screening for each study.

On the first screening, we excluded a total of 209 articles and continue to evaluate with full-text reading

of 14 articles. From 14 full-text articles, 10 articles were excluded, because the articles did not fit the eligibility criteria. On final search, a total of 4 RCT studies which fit the eligibility criteria were included in the analysis of this study.

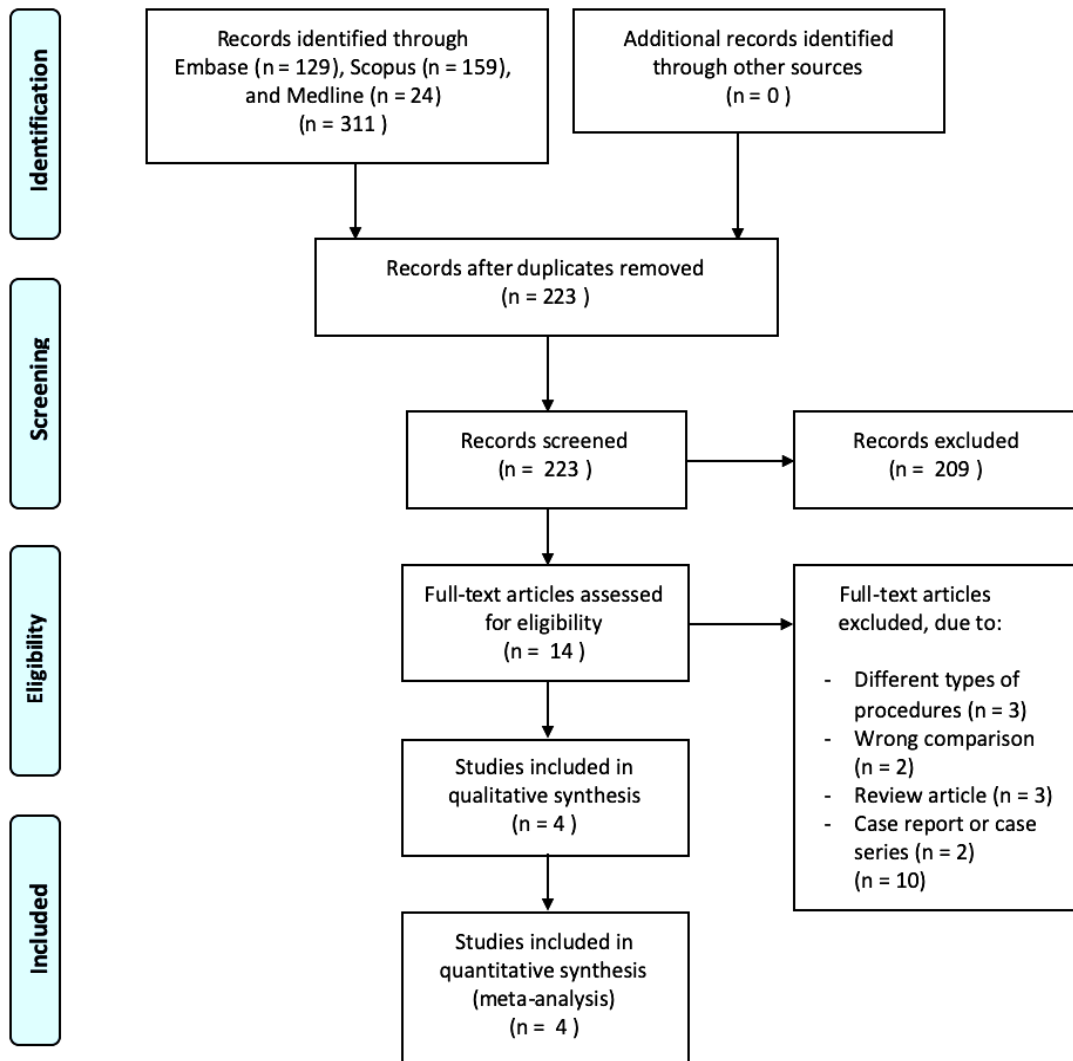


Figure 1. Screening process and identification of study summarized on PRISMA flowchart diagram

Table 1. Clinical characteristics of participants in included RCTs

Author	Type	Group	Intervention	Intervention Protocol	n	Age	Testoteron Serum (ng/mL)	Penile Length before Intervention (cm)	Penile Length after Intervention (cm)	Penile Circumference before Intervention (cm)	Penile Circumference after Intervention (cm)	Glans width before Intervention (cm)	Glans Width after Intervention (cm)	Time to Procedure	Overall Complications (n)	Complication Report
Asgari et al. 2015	RCT	Intervention	TIP Urethroplasty	Intramuscular Testoteron Enanthate	91	32.1 months	0.4	2.83	3.84	3.53	4.55	NR	NR	1 month	5	Fistula (4), Meatal Stenosis (1), Dehiscence (0), Diverticula (0)
Asgari et al. 2015 Chen et al. 2015	RCT RCT	Control	TIP Urethroplasty Flap preputial island transverse urethroplasty / Duckett and Thiersch-Duplay combination	No Hormonal Intervention	91	28.7 months	0.37	2.81	2.88	3.51	3.57	NR	NR	1 months	12	Fistula (7), Meatal Stenosis (3), Dehiscence (1), Diverticula (1)
		Intervention		Oral Testoteron undecanoate	34	21.6 months	0.032	1.93	2.99	1.14	1.44	NR	NR	3 - 6 months	5	Fistula (2), Urethral Stricture (0), Diverticula (3), Reoperation (5)
Chen et al. 2015 Kaya et al. 2008	RCT RCT	Control	Flap preputial island transverse urethroplasty / Duckett and Thiersch-Duplay combination TIP Urethroplasty	No Hormonal Intervention	36	24.2 months	0.056	NR	NR	NR	NR	NR	NR	3 - 6 months	15	Fistula (9), Urethral Stricture (3), Diverticula (3), Reoperation (14)
		Intervention		Transdermal DHT	37	30.8 months	NR	NR	NR	NR	NR	NR	NR	NR	1 month	3
Kaya et al. 2008 Menon et al. 2017	RCT RCT	Control	TIP Urethroplasty Snodgrass Urethroplasty	No Hormonal Intervention	38	35.1 months	NR	NR	NR	NR	NR	NR	NR	1 month	34	Fistula (2), Dehiscence (3), Scar (16), Reoperation (3), Meatal Stenosis (2)
		Intervention		Intramuscular Testoteron Enanthate	49	4.45 years	NR	3.6	4.7	3.9	5.2	1.5	1.8	3 months	5	Fistula (5), Dehiscence (7)
Menon et al. 2017	RCT	Control	Snodgrass Urethroplasty	No Hormonal Intervention	45	4.97 years	NR	4.1	NR	4.6	NR	1.6	NR	1-3 months	7	Fistula (7), Dehiscence (7)



Clinical characteristics of the trials

In this review, a total of 4 studies were included which evaluated 421 patients undergoing urethroplasty procedure (Asgari et al. 2015, Chao et al. 2017, Kaya et al. 2008, Menon et al. 2017). A total of 211 patients was allocated in group that received intervention, such as urethral hormone intervention, and urethral stricture.

Risk of bias assessment in RCT

The included RCTs were evaluated in terms of risk of bias with full-text reading and the application of RoB tools 2 by Cochrane Collaboration. In the bias domain due to randomization process, we found that majority of studies used randomization technique through computer. Thus, the risk of bias caused of randomization process was considered to be low in all studies except the study from Kaya et al. (2008) that did not explain randomization process adequately. In the domain bias due to deviation from intervention, we found that the risk of bias was considered to be low in all studies. Based on the assessment of risk of bias due

to the missing outcome, we found that several concerns on the study from Chen et al. (2015), Kaya et al. (2008), Menon et al. (2017), there were no adequate information regarding the number of patients that dropped out or lost to follow up. Overall, the evaluation on 4 domains showed that the risk of bias between the studies was considered low (Figure 2).

The effect of hormonal therapy to overall complications

In terms on the outcome of overall complication, the analysis of 4 RCTs which evaluated 421 patients undergoing urethroplasty procedure using pre-operative testosterone hormonal therapy was compared with control (Asgari et al. 2015, Chao et al. 2017, Kaya et al. 2008, Menon et al. 2017). Based on the result from forest plot analysis, there were significantly fewer overall complications in groups receiving pre-operative hormonal intervention compared to control group (OR=0.17; 95% CI=0.04, 0.77; p = 0.02). In this study, analysis was conducted by using random-effects DerSimonian model due to high heterogeneity among studies ($I^2 = 84\%$, $p = 0.0004$) (Figure 3).

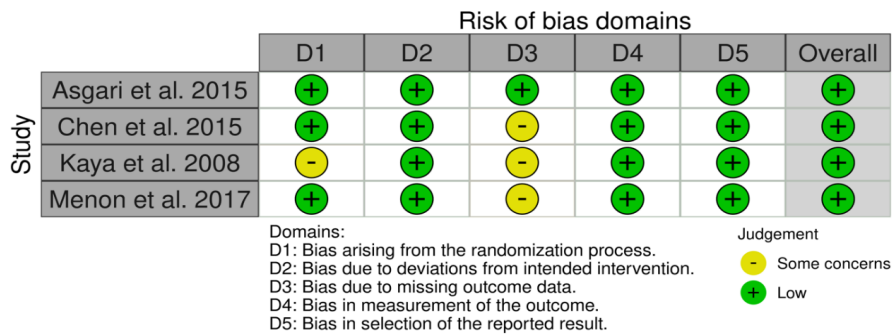


Figure 2. Risk of bias assessment using Cochrane risk of bias (RoB) tools 2

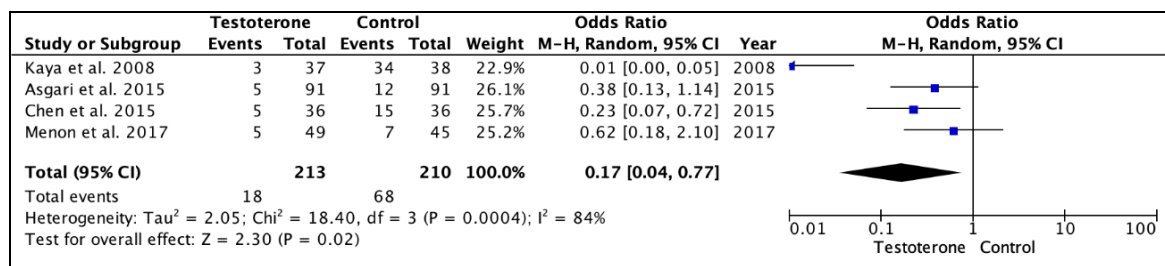


Figure 3. The result of forest plot analysis on the incidence of overall complication in groups receiving preoperative hormonal treatment compared to control



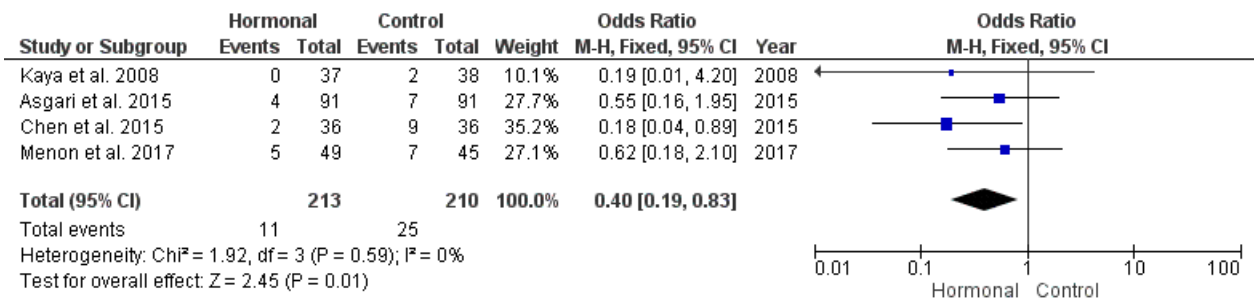


Figure 4. Forest plot analysis result on the incidence of urethrocutaneous fistula in groups receiving pre-operative hormonal therapy compared to control

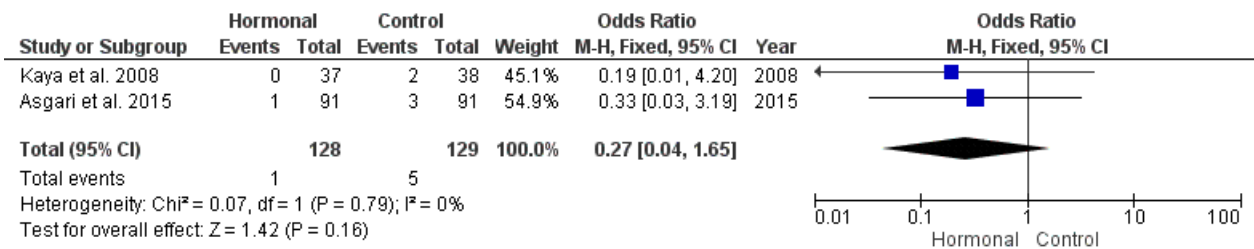


Figure 5. The analysis of forest plot on the incidence of dehiscence in groups receiving preoperative hormonal therapy compared to control

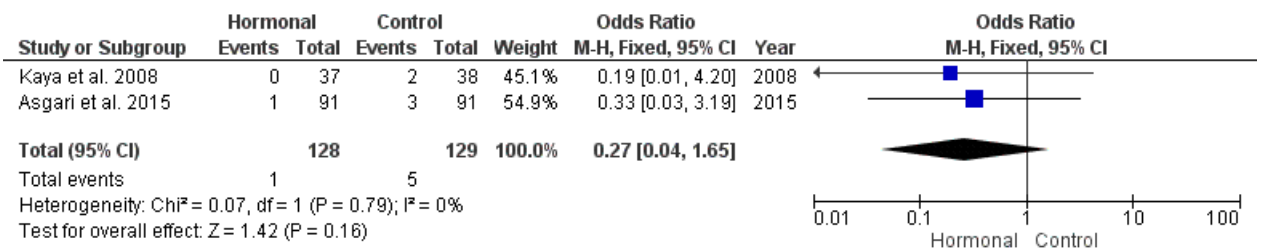


Figure 6. The analysis of forest plot on the incidence of meatal stenosis in group with preoperative hormonal therapy compared to control

The effect of hormonal therapy on the incidence of urethrocutaneous fistula

Based on data extraction that we performed, all RCTs reported the incidence of urethrocutaneous fistula. Several studies showed insignificant result on the incidence of urethrocutaneous fistula, while other studies reported the significant result. Based on final analysis, we found that hormonal therapy significantly reduced the incidence of post-operative urethrocutaneous fistula (OR=0.4, 95% C=0.19, 0.83, p=0.01). The analysis of forest plot showed that heterogeneity between included RCT studies was classified to be low with I² test of 0% and the heterogeneity p-value was 0.59, thus fixed-effect model was used (Figure 4).

The effect of hormonal therapy on the incidence of dehiscence

Based on the analysis of forest plot analysis in 3 RCT studies which evaluated the effect of hormonal therapy on the incidence of dehiscence, there were no

significant difference between the group receiving pre-operative hormonal therapy compared to without hormonal therapy (OR=0.59, 95% CI=0.23, 1.54, p=0.28). Besides, the studies had good heterogeneity with p value 0.45 and I² of 0% (Figure 5).

The effect of hormonal therapy on the incidence of meatal stenosis

There were 2 RCTs which evaluated the effect of hormonal therapy on the incidence of meatal stenosis. Based on the pooled analysis in 257 participants which were allocated in hormonal therapy group (n=128) and control group (n=129), hormonal therapy did not comprise significant effect on the incidence of meatal stenosis reduction (OR=0.277; 95% CI=0.04, 1.65; p=0.16). Heterogeneity between RCT studies was considered low with I² test of 0% and heterogeneity p value of 0.79. Thus, the analysis was using fixed-effect model (Figure 6).



DISCUSSION

One most common post-operative complication of hypospadias is suspected to be caused by surgical difficulties due to penis size. This factor becomes a burden for a surgeon to perform corrective surgery well. This difficulty may also lead to several post-operative complications, causing morbidity and a lower quality of life (Lucas et al. 2020, Ru et al. 2021). Based on these considerations, several studies have been investigating several methods to increase penis size before surgery.

Based on the mechanism of action of the hormone on penile growth and development, several studies suggested the use of pre-operative testosterone as a stimulator for increasing penis size. Several surgeons believed that pre-operative androgen administration can facilitate penile reconstruction to achieve excellent results and outcomes (Mohammadipour et al. 2020). Several studies suggested that small penis size should be considered as an independent risk factor for post-operative complications (Bush et al. 2015, Wong & Braga 2015). Before evaluating the role of testosterone in reducing post-operative complications the role of testosterone in increasing penis size has to be clear. Satav et al. (2015) discovered that both parenteral and topical testosterone may achieve the desired penis size compared to pre-testosterone administration. Previous systematic reviews on a similar topic resulted in inconsistent and various results with a low quality of evidence (Chao et al. 2017, Kaya et al. 2008, Wright et al. 2013).

In this review, we discovered that there was a significantly lower complication rate in patients receiving the role of pre-operative hormonal therapy, including testosterone and its derivatives (OR 0.17; 95% CI 0.04, 0.77; $p = 0.02$) (Asgari et al. 2015, Chen et al. 2015, Kaya et al. 2008, Menon et al. 2017) (S. A. Asgari et al., 2015; C Chen et al., 2015b; Kaya et al., 2008b; Menon et al., 2017b). A larger penis size allows for an easier surgical correction. Androgen stimulation would increase tissue size with high vascularization, which could also facilitate tissue healing. (Bastos et al. (2011) discovered that the administration of 1% testosterone ointment could increase the volume and density of blood vessels. This increase is most beneficial in patients with microphallus or who had a previous unsatisfactory outcome (Ahmad et al. 2011). Aside from the intraoperative factors, the effects would also decrease the post-operative formation of scar tissue (Bahadir et al. 2016).

We also discovered that pre-operative hormonal therapy administration can decrease the incidence of

urethrocutaneous fistula to 60% (OR 0.4, 95% CI 0.19, 0.83, $p = 0.01$), but not significant in meatal stenosis incidence ($p = 0.16$) and dehiscence ($p = 0.28$) (Asgari et al. 2015, Chen et al. 2015, Kaya et al. 2008, Menon et al. 2017). There are some negative effects of testosterone reported by studies. Several studies inhibitory effects of androgen on wound healing and increasing inflammation on tissue. Some patients also complained of penile discomfort, unwanted erection, pubic hair growth, and pigmentation (Gorduza et al. 2011).

Some studies also reported that a long-term administration of testosterone for 3 months or more could increase the rate of post-operative complications instead (Netto et al. 2013). The difference in results was due to the lack of consensus and standard regarding the type, dose, and route of administration for pre-operative testosterone in hypospadias management. Positive results from this systematic review was expected to be one of the basis for creating a recommendation regarding the pre-operative testosterone administration (Asgari et al. 2015, Kaya & Radmayr 2014). Other studies also evaluated the role of endogenous hormones, such as estradiol and B-HCG, which could also increase penis size. However, the number of studies evaluating the role of these hormones was limited (Krishnan et al. 2016). There are several limitations to this systematic review.

Strength and limitation

Due to the limited number of published RCTs, the evaluation of hormonal administration was performed on all routes of administration. There is also one study that evaluated *dihydrotestosterone* as intervention. Different types of urethroplasty were also performed by the included studies. As more published studies become available, a sub-group analysis evaluating each type of hormonal therapy can be performed. Adverse events of the intervention should also be analyzed quantitatively in the future. These side effects might affect the patient's quality of life; thus, its potential occurrence should be considered to conduct a treatment strategy.

CONCLUSION

Pre-operative hormonal therapy administration including testosterone and its derivatives may decrease the postoperative complication rate in hypospadias patients, as indicated by a lower incidence of urethrocutaneous fistula and overall complications. Further studies with a larger sample and randomized design assessing different sub-groups of hormonal therapy are required.

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Conflict of interest

None0

Funding disclosure

None.

Author contribution

All authors were conceptual idea, study design, collected data, BIP, ARDJ and ANP/analysis data. LD was write the manuscript

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