Use of Oral Ketoconazole To Prevent Postoperative Penile Erections Following Surgery For Hypospadias

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ABSTRACT

Objective — *To assess the effectiveness of oral ketoconazole in preventing postoperative penile erections after hypospadias repair.*

Study design — *Cross sectional analytic study.*

Place & Duration of study — *Department of Plastic and Reconstructive Surgery, Dow University of Health Sciences and Dr. KM Ruth Pfau Civil Hospital Karachi, from December 2019 to July 2020.*

Methods — *All patients with the diagnosis of hypospadias between the ages of 4 - 40 years were included in the study. Patients were allocated into intervention group (ketoconazole group) or control group through lottery method. Patients were assessed in postoperative period for penile erection, postoperative pain and overall satisfaction related to cosmetic appearance.*

Results — *At total of 80 patients were enrolled. They were equally divided into two groups. At first follow-up the postoperative erections were relieved in 65% patients, pain relieved in 40%, and 45% of the patients / parents reported strong satisfaction with the outcome in ketoconazole group. At third 3rd follow-up erections were relieved in 85%, pain relieved in 75% and 57.5% reported satisfaction in the intervention group which was statistically significant (p <0.001) in comparison with the control group (35%).*

Conclusion — *Ketoconazole effectively inhibited postoperative erections after penile reconstructive surgery. It may be considered as a valuable adjunct for the prevention of painful erections in the early postoperative period.*

Key words — *Ketoconazole, Penile erections, Hypospadias, Wound dehiscence, Urethro-cutaneous fistula.*

INTRODUCTION:

Hypospadias is a birth defect in which the external urinary meatus is not located at its normal position in glans penis. The meatus may be at a variable location on the ventral surface of the penis. Different surgical procedures are reported for the repair of this anomaly. A common problem encountered is the painful erections in the postoperative period in these patients.[1,2] Surgery for hypospadias has advanced throughout the years the aim of which is to achieve a straight penis without chordee, meatus at its normal or near normal position in the glans and a cosmetically acceptable appearance.[3,4]

Proximal hypospadias can be repaired by various surgical procedures that may include single stage or two stage repairs depending upon the location of the meatus.[5,6] Each procedure has its advantages and disadvantages, however not a single procedure has received broad acceptance.[7] This is reflected in more than 300 surgical procedures that are reported

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for the repair of hypospadias.[8,9]

In order to prevent postoperative penile erections amyl nitrate, sedatives, refrigerant sprinkles, dorsal nerve blocks and number of other interventions are done. However, they are not effective. Ketoconazole lowers testosterone production and acts as an anti-androgenic drug. High oral dosage of ketoconazole (up to 400mg) three times a day blocks testicular and adrenal androgen that results in a decrease testosterone level. Ketoconazole is additionally an androgen receptor blocker, thus has an additional mode of action.[10] Ketoconazole has proven to be a safe drug, and based on its anti-steroidogenic side effects, it is used in postoperative period in patients to avoid erections.[11] In literature ketoconazole is used for relieving painful erections especially in patients who suffer from ischemic painful erections.[12-14] This study was conducted to document frequency of postoperative penile erections and pain intensity associated with it as well as level of satisfaction as reported by the patients. It was also expected that the rate of urethra-cutaneous fistula formation reduce by addition of oral ketoconazole after surgery.

METHODS:

Study design, place and duration: It was a cross sectional analytic study conducted at the Department of Plastic and Reconstructive Surgery, Dow University of Health Sciences and Dr. KM Ruth Pfau Civil Hospital Karachi, from December 2019 to July 2020.

Ethical considerations: This study was approved by the Scientific Committee, Institutional Review Board, and Board of Advanced Studies and Research of Dow University of Health Sciences (Ref no. DUHS/BASR/2020/-553). Informed consent / assent was obtained from the study participants and parents.

Inclusion criteria and exclusion criteria: All male patients between of 4 to 40 years of age were included. Patients who were previously operated, psychologically challenged, with co-morbid like diabetes mellitus and hypertension, were excluded from the study.

Sample size estimation and sampling technique: The sample size was calculated using OpenEpi.com online sample size calculator using the effect size previously reported of ketoconazole in relieving erection by Hoeh MP[12] (87.5% vs 12%). Minimum required sample size was 80 patients (40 in each group) at 99% confidence level and 90% power. Non-probability consecutive sampling technique was used.

Study protocol: Patients were divided into two groups, the intervention group (ketoconazole group) and a control group. All patients were explained regarding ketoconazole drug and its effects. Lottery method was used for allocation of the groups by using sealed envelopes. Ketoconazole (2mg/kg) was given once a day to patients in intervention group two days before surgery and till 7th postoperative day. Questionnaire regarding the penile erections, postoperative pain intensity and overall satisfaction was filled on postoperative days 5, 8, and 10.

Statistical analysis: Data analyses were done using SPSS version 21. Mean and standard deviation were calculated for quantitative variables like age. Frequency and percentages were computed for penile erections, postoperative pain intensity and overall satisfaction. Chi square test was applied and p <0.05 was taken as significant.

RESULTS:

A total of 80 patients were divided in two equal groups. The mean age of the patients was 8.28±2.30 years for ketoconazole group and 9.42±2.91 years for the control group. At first follow-up erections were relieved in 26 (65%) and pain relieved in 16 (40%) patients in ketoconazole group as compared to the control group where erections persisted in all patients and pain relief was reported in six (15%) patients. This was statistically significant (p < 0.001). At second follow-up erections were relieved in 30 (75%) and pain relieved in 26 (65%) patients in ketoconazole group as compared to the control group (p=0.019). At third follow-up erections were

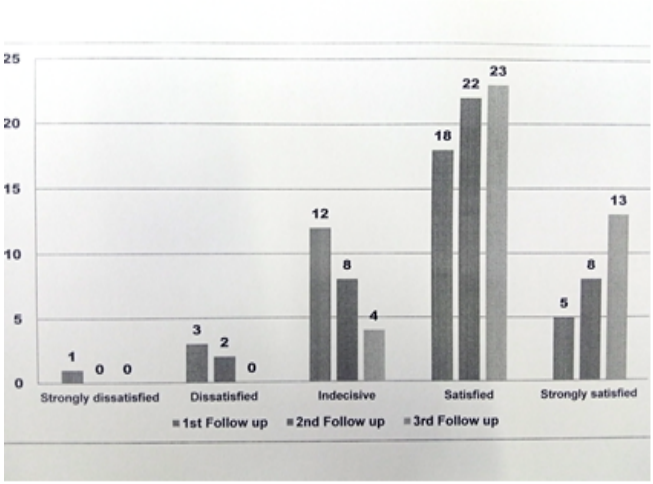

Fig I: Overall satisfaction in Ketoconazole group on 1st, 2nd and 3rd follow-ups

Table I: Erection and Pain Status At First Follow-up (5th Postoperative Day)

	Ketoconazole Group (n- 40)		Control Group (n - 40)	
Erections relieved	26	65.0%	0	0%
Pain releived	16	40.0%	06	15%
Mild pain	15	37.5%	20	50%
Moderate pain	07	17.5%	06	15%
Severe pain	02	05.0%	08	20%

Table II: Erection and Pain Status At Second Follow-up (8th Postoperative Day)

	Ketoconazole Group (n- 40) G		Control Group (n - 40)	
Erections relieved	30	75%	0	0%
Pain releived	26	65%	10	25%
Mild pain	12	30%	18	45%
Moderate pain	02	05%	07	17%
Severe pain	0	0%	05	12.5%

Table III: Erection and Pain Status At Third Follow-up (10th Postoperative Day)

	Ketoconazole Group (n- 40)		Control Group (n - 40)	
Erections relieved	34	85%	00	0%
Pain releived	30	70%	14	35%
Mild pain	10	25%	20	50%
Moderate pain	00	0%	04	10%
Severe pain	0	0%	02	05%

Table IV: Side Effects of Ketoconazole (n - 40)

	Number (%)
Headache	5 (12.5%)
Nausea	6 (15.0%)
Feet swelling	2 (05.0%)
Pruritus	3 (07.5%)
Frequent urination	2 (05.0%)
Jaundice	4 (10.0%)

relieved in 34 (85%) and pain relieved in 30 (75%) patients in ketoconazole group as compared to the control group (p <0.001). Follow-up details are given in tables I, II and III.

Eighteen (45%), 22 (55%) and 23 (57.5%) patients / parents were satisfied on 1st, 2nd and 3rd follow ups as shown in figure I. Side effects were reported in 18 (45%) patients in ketoconazole group (table IV). A 2.5% urethrocutaneous fistula rate was observed in the control group, while the no fistula was noted in ketoconazole group.

DISCUSSION:

This study reported high success rate when ketoconazole was added in the management of patients with hypospadias. This is a challenging anomaly with many controversies related to timings of surgery and choice of the surgical procedure to deal with it. Currently the surgery is preferred during infancy.[15] In this study mean age of the patients in both the groups was quite high, between 8 – 9 years. A few reports showed that in grown-up patients the chances of wound dehiscence is more.[16,17] One of the reasons for failure of the procedures in penile erections. Ketoconazole hinders conversion of progesterone to testosterone.[18,19]

Previous studies have shown that ketoconazole was effective in preventing postoperative erections. A study reported that in patients who were taking ketoconazole, 23% had no painful erections. In patients who did not receive ketoconazole 71% patients reported erections that were painful. Both studies recommended using ketoconazole for the prevention of erections.[11,13] Our study reported

comparable results as 85% reduction in erections and 75% reduction in pain were reported that was statistically significant. However, a randomized double blind trial reported that ketoconazole did not significantly prevent erections as 84% patients taking this drug had episodes of erections which was similar to the placebo group (83%). The sample size in that RCT was too small.[20] Our study provided a convincing data in favor of using ketoconazole with larger sample size.

Limitations of the study: The study participants were comparatively were older children and there was a mix of age groups. A study with a larger sample size, of uniform younger age group patients with similar variety of hypospadias would be more scientific in nature. This may be conducted as a multicenter trial.

CONCLUSION:

Ketoconazole effectively inhibited postoperative erections after penile reconstructive surgery and pain relief was reported in large number of patients with satisfactory outcome.

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Faisal Akhlaq Ali Khan: Manuscript writing .
Nasreen Bano: Data acquisition and analysis.
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