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EFFFECT OF PRIOR TESTOSTERONE THERAPY ON FUTURE TESTICULAR VOLUME & SPERMATOGENESIS IN MALE CONGENITAL HYPOGONADOTROPIC HYPOGONADISM IN A TERTIARY CARE CENTRE IN EASTERN INDIA

Endocrinology

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ABSTRACT

Gonadotropin induces masculinization and spermatogenesis in men with congenital hypogonadotropic hypogonadism (CHH) via testicular androgen production .However, large cohort studies for the efficacy and reliable predictors of this therapy need to be conducted.

Aim: The aim of this real scenario was to investigate the efficacy of gonadotropin vs gonadotropin & testosterone treatment in a cohort of male CHH patients and analyze putative predictors for successful spermatogenesis. In this study we included 7 CHH azoospermic patients without puberty development treated between 2015 and 2018. All patients received combined human chorionic gonadotropin (HCG) and human recombinant Follicular stimulating hormone(FSH) & out of 7 three patient received testosterone plus gonadotropin(TGT) , the testosterone therapy was omitted at least 3 month before the gonadotropin therapy(GT) and were followed up for 3 monthly . Serum total testosterone level, testicular volume , spermatogenesis, were recorded at each visit.

Results: The mean Age were 23 ± 2.48 & 25.3±1.45 in GT and TGT group respectively which has the p value of >0.05. After gonadotropin therapy, testicular size was enlarged from 2.03±.20 to 5.93 ± 1.36 mL (P<0.0001) in GT & 8±1.6 ml (P0.0001) in TGT and the serum total testosterone was elevated from 14.95±0.97 to 364±129 ng/dl/L (P<0.001) in GT &. 588±233 (P0.0001)ng/dl in TGT . There were no singnificant diffence in TV and testosterone among T and TGT patients .

Spermatogenesis occurred in both group with a mean value of 0 (p 0.00001) , 12.5(p >0.05), 22.6 (p>0.05) million/ml at baseline , GT & TGT groups respectively.

Conclusion : In this scenario the TGT therapy associated with numerically more increase in the testicular size & spermetogenesis as comprared to GT arm but this difference is not statistically significant .We found no adeverse effect of testosterone therapy on the spermatogenesis.

KEYWORDS

Testosterone , Gonadotropin ,Spermatogenesis , Testicular Volume

INTRODUCTION :

Congenital Hypogonadotropic Hypogonadism (CHH), caused by deficiency or dysfunction of Gonadotropin-releasing hormone (GnRH), is a disorder characterized by delayed puberty and infertility. The incidence of CHH is 1–10:100,000 in live births. Gonadotropin induces masculinization and spermatogenesis in men via intra testicular androgen production (1). The normal development of fertility needs pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH), which stimulates the synthesis of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) from the anterior pituitary. Gonadotrophins stimulate gonadal testosterone production and spermatogenesis. LH stimulates testicular Leydig cell proliferation and testosterone secretion, whereas FSH induces the development of spermatogenesis via the activation of sertoli cells (5,6) The both LH and FSH are the primary hormonal factors regulating testicular functions required for male fertility, via the hypothalamic-pituitary-gonadal (HPG) axis. Failure of this axis, such as disrupted GnRH or gonadotrophin secretion, leads to clinical hypogonadotropic hypogonadism (HH)(7). HH may be either acquired or congenital and is a relatively rare cause (<1%) of male infertility. A congenital form of HH accompanied with anosmia is referred to as Kallmann syndrome(8) However, induction of puberty with gonadotropin therapy is cumbersome due to frequent injection, high cost and compliance issues as compared to testosterone therapy. Testosterone is used in male with delayed puberty to induce secondary sex characters but the effect of testosterone on future spermatogenesis is not established. When fertility is required, pulsatile GnRH infusion or combined human chorionic gonadotropin (HCG) and human menopausal gonadotropin (HMG) therapy may promote spermatogenesis (2) Combination of gonadotropins can also induce spermatogenesis in patients with acquired hypogonadotropic hypogonadism (HH) of various causes, such as surgery for pituitary tumors, sellar radiation, and sellar craniopharyngioma (3-4).

MATERIALS AND METHODS:

Type of study : clinical prospective followup

Place of study : Medical collage kolkata

Duration of study : december 2016 to December 2018

Inclusion criteria :

CHH azoospermic patients

Diagnosis of CHH was made if a patient met all of the following criteria:

Male patients above 18 years without pubertal development

Total Testosterone level <100ng/dl

Low or normal level of gonadotropin

Normal level of other pituitary hormone

Negative findings in sellar magnetic resonance imaging (MRI).

Clinical presentations, cryptorchidism, medical history as well as family history were recorded

Sample size : total subject were 07 .

Out of 7, three patients received testosterone followed by gonadotropin therapy (TFGT) while four patients received only gonadotropins. . All patients received combined human chorionic gonadotropin (hCG 2000IU) and rhFSH (75IU) .Testosterone was omitted at least 3 months prior to initiating gonadotropin therapy (GT) .Patients were followed 3 monthly for 1 year for Clinical parameters ,secondary sexual characters, testicular volume ,Serum total Testosterone and Semen Analysis.Ethical clearance done by ethical committee of MCH kolkata.

Statistical analysis: The Statistical Package of Social Sciences (SPSS) for Windows version 20 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. We divided patients into two groups based on the type of therapy. Categorical variables were presented as numbers and percentages and compared using the Chi-square test. Continuous variables were presented as means and standard deviations and compared using the independent sample t-test. Dependent variables were examined by paired samples t-test. Statistical significance was considered when the two-tailed value of P < 0.05.

RESULTS:

The mean Age were 23 ± 2.48 & 25.3±1.45 in GT(gonadotropin

therapy) and TGT(testosterone followed by gonadotropin therapy) group respectively which has the p value of >0.05(table01).There was no effect of testosterone on testicular volume(table02). After gonadotropin therapy, testicular size was enlarged from 2.03±.20 to 5.93 ± 1.36 mL (P<0.0001) in GT & 8±1.6 ml (P0.0001) in TGT and the serum total testosterone was incresed from 14.95±0.97 to 364±129 ng/dl/L (P<0.001) in GT &. 588±233 (P0.0001)ng/dl in TGT(table 04&05)) . There were no singnificant diffence in testicular volume and testosterone among GT and TGT patients .Spermatogenesis occurred in both group with a mean value of 0 million/ml (p 0.00001) , 12.5million/ml (p >0.05), 22.6 (p>0.05) million/ml at baseline , GT & TGT groups respectively(table06).

Table 01. Baseline characteristics

	Testosterone followed by Gonadotropin Therapy N=03	Gonadotropin Therapy N=04	P
Mean Age(year)	19.00±1.00	23±4.97	0.49
Mean Tv(ml)	2.17±0.29	1.94±0.72	0.63
Mean T(ng/dl)	15.60±1.25	14.48±3.40	0.62
Mean LH(miu/ml)	0.15±0.22	0.1±0.09	0.69
Mean FHS (miu/ml)	0.4±0.26	0.55±0.32	0.54

Table 02 : effect of testosterone on testicular volume

	Testosterone followed by Gonadotropin Therapy N=03	Gonadotropin Therapy N=04	P
Mean Age(year)	19.00±1.00	23±4.97	0.49
Mean Tv(ml)	2.17±0.29	1.94±0.72	0.63
Mean T(ng/dl)	15.60±1.25	14.48±3.40	0.62
Mean LH(miu/ml)	0.15±0.22	0.1±0.09	0.69
Mean FHS (miu/ml)	0.4±0.26	0.55±0.32	0.54

table 03

Effect of Therapy on the Pubic hair staging, Testicular volume ,Serum Testosterone & spermatogenesis

NO.	Patient	Inj Testosterone 250mg/twk	Recombinant HCG 2000 IU M W F	Recombinant FSH 75 IU T T S	TV ml	Mean Tv (ml)	P S-S	T ng/dl	Sperm count million/ml
Group:01 Testosterone followed by Gonadotropin therapy									
1	IHH	3yr	3yr	3yr	RT-6 LT-5	5.5	3	234	0
2	IHH	2yr	3yr	3yr	RT-7 LT-8	7.5	4	502	18
3	IHH	3yr	3yr	3yr	RT-12 LT-10	11	5	1028	50
Group :02 Gonadotropin Therapy									
1	Kallman syndrome	NIL	3yr	3yr	RT-4 LT-4.5	4.25	3	108	0
2	IHH	NIL	3yr	1 yr	RT-4 LT-5	4.5	4	234	0
3	IHH	NIL	3yr	3yr	5-10	10	5	708	44
4	IHH	NIL	3yr	3yr	RT-3 LT-4	5	4	406	12

table04

Group:01 Testosterone followed by Gonadotropin therapy

	Before the Therapy N=3	After the Therapy N=3	P
Mean Tv(ml)	2±0	8±2.78	0.02
Mean T(ng/dl)	15.60±1.25	588±488.93	0.03
Sperm Count(million/ml)	0	22.67±25.32	

table 05

Group :02 Gonadotropin Therapy

	Before Gonadotropin Therapy	After the Gonadotropin Therapy	P
Mean Tv(ml)	1.94±0.72	5.94±2.73	0.03
Mean T(ng/dl)	14.48±3.40	364±259.83	0.04
Sperm Count(million/ml)	0	14±20.79	

table 06

Effect of treatment on the Spermatogenesis

	0 million /ml	>5million/ml	>10 million /ml	>20 million/ml
Gonadotropin (n 4)	2	0	1	1
Testosterone /// b gonadotropin (n 3)	1	0	1	1

Fischer Exact p 0.629

DISCUSSION:

In our study testosterone followed by gonadotropin therapy associated with numerically more increase in the testicular size & spermetogenesis as comprared to gonadotropin therapy alone but this diffrence was not statistically significant. We found no adeverse effect of testosterone therapy on the spermatogenesis.

The median duration of sperm production in our study was one year after the initiation of gonadotropin therapy and the most of the patient presented late in illness .

In our study none of the patient had cryptorchidism , so its effect could not be evaluated .

Conclusion :

In this scenario the TGT therapy associated with numerically more increase in the testicular size & spermetogenesis as comprared to GT arm but this diffrence is not statistically significant .We found no adeverse effect of testosterone therapy on the spermatogenesis.

Limitation of the study : Less number of subjects .

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