International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Rahman F et al. Int J Reprod Contracept Obstet Gynecol. 2022 Oct;11(10):2594-2599
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20222368

Original Research Article

Lisinopril, an angiotensin converting enzyme inhibitor for the treatment of idiopathic oligospermia: a randomized controlled trial

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Received: 28 August 2022
Accepted: 12 September 2022

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ABSTRACT

Background: Oligospermia or low concentration of sperm is a common finding in male infertility. Alterations in the expression of angiotensin converting enzyme (ACE) may be one of the mechanisms underlying male infertility and ACE inhibitors may improve the sperm count. The objective was to compare the effects of lisinopril and zinc-folic acid with zinc-folic acid alone on idiopathic oligospermia in infertile males.
Methods: This randomized controlled trial was conducted in the Department of Reproductive Endocrinology & Infertility of a medical university from March 2021 to February 2022. A total 78 diagnosed cases of infertile males with idiopathic oligospermia were selected for this study. Eligible men who gave their informed consent were randomly allocated to receive either a combination of low dose lisinopril (2.5 mg) and zinc-folic acid or zinc-folic acid alone for 12 weeks. Pretreatment and post treatment semen parameters, including sperm concentration, sperm motility and total motile sperm count were assessed.
Results: There was significant rise in sperm concentration and total motile sperm count in both groups but the mean difference in sperm concentration (2.36±2.04 vs 1.53±1.8 million/ml) and total motile sperm count (11.64±8.28 vs 9.95±6.11 million) were higher in those receiving Lisinopril in addition to zinc folic acid. The percentage increase of sperm count was higher (22.65 vs 16.70 million) in this group. Normalization of sperm count (sperm count ≥15 million/ml) was also higher in this group (18.4% vs 8.3%) with relative risk 2.21, 95% CI (0.648-4.56 %).
Conclusions: Lisinopril given orally at the dosage of 2.5 mg/day with zinc-folic acid for 12 weeks appears to be well tolerated among men with oligospermia and improves sperm count by a small margin when compared to zinc folic acid only.

Keywords: Male infertility, Oligospermia, ACE inhibitors, Lisinopril

INTRODUCTION

ACE inhibitors like lisinopril may have an effect on male infertility. The renin angiotensin system affects reproductive system of human.[1] Effect of kinins and other components of the Kallikrein-Kinin system on sperm motility and fertility related functions have been reported.[2] We know ACE inhibitors block the conversion of Angiotensin I to Angiotensin II. The latter inhibits Leydig cell function and suppresses testosterone.[3] A review of the studies of various types of ACE inhibitors on sperm count and quality carried out in animals revealed a near-consistent finding of improvement.[4] This is thought to be brought about by ACE Inhibitors blocking the conversion of bradykinin of the related Kallikrein-Kinin system to inactive peptides.[5] When it accumulates, bradykinin activates Sertoli cell functions and spermatogenesis.

Oligospermia (low sperm count) of unknown cause occurs in up to 60% of men with abnormal semen parameters.[6] The treatment of male factor like idiopathic oligospermia usually needs either empirical therapy or assisted

reproduction like intrauterine insemination or in vitro fertilization. Assisted reproductive procedures are costly and expose the couples to the risks of multiple pregnancy and other complications. Irani et al described in a review article that supplementation with folate plus zinc had a statistically significant benefit to sperm concentration, morphology when compared to the placebo.[7]

Lisinopril is an ACE inhibitor currently used to treat high blood pressure. It does not cause hypotension if given in low dose, only dry cough in some patients has been reported which can be treated by simple medication.[6] A pilot study by Mbah et al showed that the use of angiotensin converting enzyme inhibitor lisinopril improved sperm quality and quantity in oligospermic men.[6] The study has shown an increase of 6.7 million/ml of sperm count with improvement of motility and morphology of sperm over four years of treating with low dose lisinopril. Our preliminary study design was a randomized controlled trial to see whether lisinopril improves idiopathic oligospermia or not. This study was conducted to compare the effect of lisinopril and zinc-folic acid combination in idiopathic oligospermia to a control group using the traditional zinc folic acid combination alone.

METHODS

The open label parallel design randomized controlled trial was conducted in the Department of Reproductive Endocrinology & Infertility of Bangabandhu Sheikh Mujib Medical University from March, 2021 to February, 2022. The participants were infertile males age 20-45 years with oligospermia (sperm count 5-15 million/ml). The exclusion criteria were azoospermia, severe oligospermia (sperm count <5 million/ml), fever or antibiotic treatment in last 2 months, serum testosterone <300 ng/dl, serum FSH and LH <2 IU/l or >10 IU/l, any abnormality on scrotal examination and sonogram, body mass index (BMI) <18, >30 kg/m^2, known case of medical disease like diabetes mellitus, hypertension, kidney disease and demonstrable cause of infertility in female partners. The study was approved by institutional review board. Informed consent was taken from each participant.

The participants were randomized into experimental and comparator groups. Random sequence generation was done by computer generated random numbers. Permuted block randomization was done with stratification for age. Random allocation of treatment was done by someone not involved with the care of the patients. Allocation concealment was done by sequentially numbered sealed opaque envelops; each had a card inside labeled with an alphabet representing the intervention type. Allocation was never changed after opening the closed envelops. The experimental group A was given lisinopril 2.5 mg orally once a day in the morning plus 20 mg of zinc and 5 mg of folic acid in the evening for 12 weeks. The comparator group B was given 20 mg of zinc and 5 mg of folic acid in the evening for 12 weeks. All participants were instructed not to take any medications during the trial without consultation with the primary investigator. Semen analysis was done by Makler counting chamber. Response was assessed by semen analysis after 3 months. The participants were contacted every month to check for compliance.

Oligospermia was defined when the sperm count was five to fifteen million/ml. An average of the two values of two subsequent semen analysis at least one months apart was taken as baseline. There were no associated endocrine or anatomic abnormalities. Primary outcome variable was sperm concentration and secondary outcome variables were total motile sperm count (sperm concentration x semen volume x percentage progressive motility) and normalization of sperm count (>15 million/ml).

All data were collected by the principle investigator. There was no blinding. The semen analysis was done in the same laboratory by the same person thus eliminating inter-observer variability.

Sample size of participants was calculated as thiry-nine in each group, for a power of 0.80, a significance level of 0.05 and an effect size of 1.67. Statistical analyses were carried out by the SPSS program for Windows, version 22.0 (SPSS, Chicago, IL). The data were tested for homogeneity prior to analysis. The mean ± SD values or median, interquartile range were calculated as appropriate for outcome variables. Data was tested using the parametric tests such as Un-paired t test, paired t test, non-parametric test as Mann Whitney U test and Chi-square test as appropriate. P value of<0.05 was considered as statistically significant. Binary logistic regression analysis was done to assess the predictability of the dichotomous outcome variable.

RESULTS

A total of seventy infertile males with idiopathic oligospermia were randomized into two groups: thirty-nine in group A (lisinopril and zinc-folic acid) and thirty-nine in group B (Zinc-folic acid alone). One participant in group A and three participants in group B were lost to follow up, so that thirty-eight participants in group A and thirty-six participants in group B completed the study and were included in final analysis. Table 1 describes the socio-demographic characteristics of study participants. Table 2 describes the endocrine characteristics of the study participants. There is no significant difference between the two groups regarding the baseline socio-demographic and endocrine profiles. Table 3 shows that there is no significant post treatment change in blood pressure in any group.

Table 4 shows that in group A (lisinopril and zinc- folic acid), the mean sperm concentration (12.79±2.72 vs 10.42±1.90 million/ml) and total motile sperm count (22.78±10.48 vs 11.12±3.90 million) were significantly increased post treatment (at twelve weeks) from baseline. Table 5 shows that in group B (Zinc- folic acid alone), the

mean sperm concentration (11.97±2.46 vs 10.46±1.54 million/ml), total motile sperm count (21.11±7.80 vs 11.16±3.44 million) were significantly increased post treatment (at twelve weeks) from baseline. Comparing the findings of both groups, the increase in sperm count (2.36±2.04 vs 1.53±1.8 million/ml) was higher in group A (lisinopril and zinc-folic acid) compared to group B (zinc-folic acid alone). The effect size or magnitude of difference was higher (1.15 vs 0.85) in group A than in group B. So, the lisinopril and zinc folic acid was slightly more effective than zinc folic acid only.

The magnitude of increase is also measured in terms of percentage increase in sperm count. Table 6 shows that the percentage increase of sperm count was higher in group A than group B, but the rise was statistically significant (<0.05) in moderate oligospermia. Table 7 shows that normalization of sperm count (sperm count ≥15 million/ml) was higher in group A than group B (18.4% vs 8.3%) with relative risk 2.21, 95% confidence interval 0.648-4.56. A binary logistic regression was performed to ascertain the effect of treatment type, baseline sperm concentration, age and body mass index (BMI) on the likelihood that the participants will have normalization of sperm count to normozoospermia (sperm count >15 million/ml). The predictability of all the variables was non-significant except for baseline sperm concentration. One unit rise in baseline sperm concentration was associated with 2.21 times increase in the likelihood of improvement, when controlled for the effect of other variables.

P value was reached from Mann Whitney U test, a non-parametric test as distribution was non-Gaussian.

So, angiotensin converting enzyme inhibitor lisinopril combined with zinc folate had better effects on oligospermia than zinc folate alone. There was no serious side effect of any drug.

Table 1: Socio-demographic characteristics of the study participants, (n=39).

Socio-demographic characteristics	Group A (Lisinopril and zinc- folic acid)		Group B (Zinc-folic acid alone)		P value
	N	%	N	%	
Age (years)					
21-30	14	35.9	12	30.8	0.573
31-40	25	64.1	27	69.2	
Mean±SD	32.3	±4.6	32.7	±4.2	
Range (min-max)	23.0	-40.0	23.0	-39.0	
Occupational status					
Farmer	10	25.6	10	25.6	0.667
Service	23	59.0	20	51.3	
Business	6	15.4	9	23.1	
Residence					
Rural	13	33.3	15	38.5	0.637
Urban	26	66.7	24	61.5	
Socioeconomic status					
Lower	5	12.8	4	10.3	0.904
Middle	29	74.4	29	74.4	
Upper middle	5	12.8	6	15.4	
BMI (kg/m^2)					
18.5-24.9	16	41.0	21	53.8	0.829
25.0-29.9	23	59.0	18	46.2	
Mean±SD	24.9	±2.5	24.8	±2.3	
Range (min-max)	18.8	-25.9	19.0	-25.4	

Table 2: Endocrine profiles of the study participants, (n=39).

Variables	Group A (Lisinopril and zinc-folic acid)		Group B (Zinc-folic acid alone)		P value
	Mean	±SD	Mean	±SD	
FSH (mIU/ml)	5.24	±0.98	5.06	±1.29	0.494
LH (mIU/ml)	6.53	±1.59	6.25	±1.55	0.429
TSH (µIU/ml)	2.38	±0.84	2.16	±0.72	0.219
Serum testosterone (ng/dl)	765.5	±304.9	761.0	±326.7	0.951
Prolactin (ng/ml)	4.41	±1.83	4.60	±2.03	0.657

Table 3: Pretreatment and post treatment blood pressure of study participants, (n=39).

Variables	Group A (Lisinopril and zinc-folic acid), mean ± SD	Group B (Zinc-folic acid alone), mean ± SD	P value
Pre-treatment			
Systolic BP (mmHg)	110.7±11.0	110.4±12.8	0.887
Diastolic BP (mmHg)	73.8±7.0	74.1±7.5	0.877
Post-treatment			
Systolic BP (mmHg)	110.1±11.4	109.7±12.8	0.885
Diastolic BP (mmHg)	73.2±7.1	74.3±7.8	0.509

Table 4: Pre-treatment versus post treatment sperm count in group A (Lisinopril and zinc-folic acid).

Variables	Baseline, (n=39)		At 12 weeks, (n=38)		Mean diff. ±SD	95% CI of difference		P value	Effect size
	Mean	±SD	Mean	±SD		Lower	Upper		
Sperm conc. (million/ml)	10.42	±1.90	12.79	±2.72	2.36±2.04	1.69	3.04	0.001	1.15
Total motile sperm count (million)	11.12	±3.90	22.78	±10.48	11.64±8.28	8.91	14.36	0.001	1.40

Table 5: Pre-treatment and post treatment sperm count in group B (Zinc-folic acid alone).

Variables	Baseline, (n=39)		At 12 weeks, (n=36)		Mean diff. ±SD	95% CI of difference		P value	Effect size
	Mean	±SD	Mean	±SD		Lower	Upper		
Sperm con. (million/ml)	10.46	±1.54	11.97	±2.46	1.53±1.8	0.92	2.13	0.001	0.85
Total motile sperm count (million)	11.16	±3.44	21.11	±7.80	9.95±6.11	7.88	12.02	0.001	1.60

Table 6: Percentage increase in sperm count compared between two groups.

Variables	Group A (Lisinopril and zinc-folic acid), (n=38), median, interquartile range	Group B (Zinc-folic acid alone), (n=36), median, interquartile range	P value
Percentage increase in sperm count (moderate oligospermia 5-<10 million/ml), n=23	25 (17.35-37.5)	12.5 (0-12.5)	0.021
Percentage increase in sperm count (mild oligospermia 10-<15 million/ml), n=51	20 (8-30)	16.7 (5.77-30)	0.355

Table 7: Normalization of sperm count compared between the two groups.

Variables	Group A (Lisinopril and zinc-folic acid), (n=38)		Group B (Zinc-folic acid alone), (n=36)		Relative risk	95% CI	
	N	%	N	%		Lower	Upper
Normalization (sperm count ≥15 million/ml)	7/38	18.4	3/36	8.3	2.21	0.648	4.56

Table 8: Distribution of study subjects according to side effects, (n=74).

Side effects	Group A (Lisinopril and zinc-folic acid), (n=38)		Group B (Zinc-folic acid alone), (n=36)		P value
	N	%	N	%	
Dry cough	2	5.3	1	2.8	0.521^{ns}
Weakness	1	2.6	0	0.0	0.514^{ns}

ns=not significant, p value reached from Chi square test

DISCUSSION

The pathophysiological mechanisms involved in abnormal semen parameters in most cases are complex and far from being well understood. Toshimori et al.[8] Oligospermia of unknown cause is a commonly encountered form of male infertility and Cavallini et al and it poses a major therapeutic challenge.[9] Antioxidants, hormones and dietary supplements have been used but not with very encouraging results. When drug treatments for infertility fail, intrauterine insemination and assisted reproductive therapies such as in vitro fertilization and intracytoplasmic sperm injection are recommended. ACE inhibitor is a new empirical therapy tried in our study. The objective of the study was to compare the effects of lisinopril and zinc-folic acid with zinc-folic acid alone on idiopathic oligospermia in infertile males. The increase in sperm concentration and total motile sperm count were higher in men given lisinopril in addition to zinc folic acid.

Preclinical animal studies of the effect of Lisinopril on semen parameters were done by Okeahialam et al and Saha et al.[11] Okeahialam et al did their study on rat model given varying doses of Lisinopril for 35 days.[10] The drug appeared to improve sperm count and motility in a dose dependent manner. Saha et al studied the rats given lisinopril for variable terms in variable doses and reported a marked increase in sperm density and sperm motility.[11] This is thought to be brought about by ACE inhibitors blocking the conversion of bradykinin of the related Kallikrein-Kinin system to inactive peptides.[2] ACE inhibitors are Kinin enhancing drugs and kinins like kallikrein are effective in improving sperm count and sperm motility.[12]

Possible use of antihypertensive agents in infertile males was prompted by 2 separate observations in 2 hypertensive male patients who had long-standing infertility and azoospermia of unknown cause. In both men, there was normalization of semen parameters apparently resulting from therapy with 2.5 mg daily doses of lisinopril, and spouses of both men became pregnant.[6] Pilot study conducted by Mbah et al was a randomized, placebo-controlled, crossover trial on 33 men with idiopathic oligospermia having either daily oral lisinopril 2.5 mg (n=17) or daily oral placebo (n=16).[6] Age group was comparable to that in our study, 26.93±7.3 and 30.86±8.8 years in treatment and placebo group respectively. However, baseline sperm counts were lower than that in our study; 7.43±3.97 and 5.29±2.6 million/ml in treatment and placebo group. The cross over point was at 96 weeks and end point at 281 weeks. The 4 years' follow up study revealed an increase in sperm count, motility and morphology and reported normalization of semen parameters in 53.4% and pregnancy rate in 48.5%. Beneficial effect of lisinopril is not that apparent in our study. This may be explained by short duration (12 weeks only) of study.

In this study the comparator arm of study participants was given zinc-folic acid alone. The sperm concentration and total motile sperm count were significantly increased after 12 weeks treatment. A systematic review on the effect of zinc and folate supplementation in infertile males concluded that there is significant rise in sperm concentration with the treatment.[7] The experimental arm given lisinopril had co treatment with zinc folate in our study. The effect of lisinopril may be overshadowed by the effect of co treatment.

The effect size measures the magnitude of difference. The effect size as measured by Cohen'sd or standardized mean difference in sperm count over 12 weeks was more in Lisinopril and zinc-folate group compared to that in zinc folate group. So, the lisinopril and zinc folic acid may be slightly more effective than zinc folic acid only. A high p value may be because of a small sample size when the effect size is small. The percentage increase in sperm count was more in the men given lisinopril. If normalization of sperm count was considered a more clinically relevant outcome it was 2.21 times more in men give lisinopril though the change was best predicted by a higher baseline sperm count. As one of the few human studies done to see the effect of ACE inhibitors on semen parameters, our study reveals that some benefit, albeit limited can be expected with the use of ACE inhibitors in infertile males. This should be kept in mind while choosing anti-hypertensive drugs for men who also have abnormal semen parameters.

Regarding side effects, 5.3% of men given lisinopril in the present study had dry cough compared to the 7.8% in the study done by Mbah et al.[6] Cough is known to be one of the most troublesome side effects of ACE inhibitors (including lisinopril). There were no other serious side effects in the study by Mbah et al as well.[6]

Limitations

The study was limited by small sample size, short study period, study population recruited from one selected center challenging the external validity of study findings and the use of zinc folic acid as co treatment and control instead of placebo. Selection bias was eliminated by random allocation and allocation concealment but there was absence of blinding of participants and personnel dispensing the drugs and absence of blinding of outcome assessment. Outcome data was incomplete as there was drop out of participants in both arms.

CONCLUSION

Lisinopril given orally at the dosage of 2.5 mg/day with zinc-folic acid for 12 weeks appears to be well tolerated among men with oligospermia and improves sperm count by a small margin when compared to zinc folic acid only. Larger, multicenter, randomized, placebo-controlled studies with longer duration on the efficacy and safety of

ACE inhibitors in infertile men may bring up the results more clearly.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Rahman F, Ishrat S, Halder S, Nasrin I, Amir M. Lisinopril, an angiotensin converting enzyme inhibitor for the treatment of idiopathic oligospermia: a randomized controlled trial. Int J Reprod Contracept Obstet Gynecol 2022;11:2594-9.