Section: General Surgery

Original Research Article

A STUDY OF MULTIPLE INTRA-PROSTATIC OZONE INJECTION IN BPH PATIENTS

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Abstract

Background: Transurethral resection of the prostate remains the gold standard therapy for decades. Ozone gas, when injected intraprostatic ally was identified as alternative non-surgical minimally invasive treatment. We had studied the role of multiple doses of intraprostatic ozone injection on prostate volume reduction as compared to single dose. **Materials and Methods:** Fifty patients of BPH who had prostate size more than 30 grams with retention in which alpha blocker trial had failed were included in the study. 40 ml of Ozone gas at concentration of 30ug/ml (generated by medical grade ozone generator) was instilled in the prostate (IPOI) per rectally at 4 points. Patients who failed to improve are subjected to repeat episodes of IPOI in a similar way. Maximum of 3 sessions of IPOI were given. Ultrasonography was done weekly for three weeks of intraprostatic ozone injection to assess the prostatic volume (in cc). **Results:** Total 50 patients, mean age 65.8 years were included in the study. Mean prostate volume was found to be 53.9cc, 53.69cc and 52.75cc after 1st, 2nd and 3rd dose respectively. There was significant reduction in prostate volume after 3 weeks duration ($p=0.0005$). The mean prostate volume reduction was significantly more in successful voiders (mean=6.64) as compared to non voiders (mean=3.19).($P<0.0001$). **Conclusion:** Multiple doses of intra prostate injection is a good, cost effective, safe and minimally invasive procedure as compared to single dose. It can be helpful in some patients who have failed trials without catheter even on alpha blockers and are unfit for TURP. Large sample size and long term results are required to assess its efficacy and usefulness.

INTRODUCTION

Benign prostatic hyperplasia contributes a lot to lower urinary symptoms in aging men. Transurethral resection of the prostate remains the gold standard therapy for decades. Pharmacotherapy recommended for BPH include alpha blockers, 5 alpha reductase inhibitors, and numerous plant extracts had largely replaced the surgical treatment but were not always successful in every patient of BPH. Associated comorbid conditions and morbidity of the surgical procedure sometimes require an alternative nonsurgical minimally invasive treatment to reduce the prostate size.

Ozone gas is used in the treatment of certain medical conditions utilizing its anti-inflammatory properties. It was used in protruded disc for dissection as a treatment of prolapsed intervertebral disc cases. The effect of ozone motivated Vitoria.[2] to use ozone in few patients with BPH for symptomatic improvement. This study was carried out on the basis of this hypothesis.

We had studied the said effect of ozone on prostate size reduction by intraprostatic ozone injection (IPOI). Patients were assessed for prostate size reduction and successful trial without catheter (TWOC) after IPOI.

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MATERIALS AND METHODS

The study was conducted in the department of surgery, NSCB Medical College Jabalpur (M.P.) in a tertiary care hospital. It is a prospective study which was done from March 2017 to August 2018. Patients of BPH with retention in whom alpha blocker trial has failed were included. Inclusion criteria - All patients of BPH in whom trial without catheter (TWOC) after alpha blocker had failed and having normal PSA values, Prostate of size 30 grams or more, Patients not fit for anesthesia ,Patients who are willing for ozone therapy after explaining standard treatment of BPH (TURP).Exclusion criteria -Any patients with concomitant bladder pathology were excluded such as neurogenic bladder, Patients who are having any evidence of Ca prostate.

All patients fulfilling the inclusion criteria underwent systemic assessment. History was taken and symptoms were noted. Pre procedural assessment-Clinical - clinical assessment was done by digital rectal examination. In DRE we are assessing surface (smooth/rough), consistency (firm/hard), overlying mucosa (freely mobile/fixed) and grade of prostate (grade-1, grade-2, grade-3), which helps us to making conclusion that prostate enlargement is either benign or malignant in nature ,Radiological - radiological assessment was done by using ultrasonography. In ultrasonography assessed volume of prostate and PVRV (post voiding residual volume). It is also helpful for assessing back pressure changes in bladder, ureter and kidney due to BPH.

Other - We are also assessing serum PSA level of patients which gives idea about benign or malignant nature of prostate as well as we can assess treatment response. Its value ranges from 0 to > 100 (0-4 ng/dl normal, 4-10 ng/dl BPH or equivocal, 10-30 ng/dl more towards Ca prostate, .30ng/dl more likely to be malignant).

Procedure of instillation -In these patients IPOI (intraprostatic ozone injection) given per rectal under finger guidance. Ozone was generated by a medical grade ozone generator (WATERHOUSE COMPANY) at the concentration of 25-30 ug/ml.

Patient is placed in the left lateral position on the operating table, both lower limb flexed at thigh and knee. DRE was done by the left index finger and located lateral lobes of the prostate. In all the selected patients 40ml of ozone at concentration of 30ug/ml was injected, 10ml at 4 points through 22 French spinal needles.

Patient was observed for 30min after giving intraprostatic ozone injection. TWOC (Trial without catheter) was given after 1 week of IPOI, size of prostate was assessed after 1 week of IPOI. Patients were assessed for symptomatic improvement.

Size of prostate was assessed after 1 week of IPOI, TWOC (trial with catheter) was given after 1 week of IPOI. Patients who failed to avoid it are subjected to repeat episodes of IPOI in similar ways. Maximum of 3 sessions of IPOI were given. Repeat dose was not given to successful voiders.

Points of assessment - Complete prostatic assessment was done byTrial without catheter (TWOC) - Trial without catheter was given after 1 week of intraprostatic ozone injection. Patients who were voided successfully, another dose of intraprostatic ozone injection was not given. Patients who failed to avoid it are subjected to repeat episodes of IPOI in similar ways. Maximum of 3 sessions of IPOI were given. Ultrasonography - ultrasonography was done after 1 week of intraprostatic ozone injection to assess the prostatic size and note the increase or decrease in prostatic volume (in cc). Especially assess and compare voiders and non-voiders. Subjective analysis-assessment is done by symptoms relieved after ozone therapy like relief from urinary retention, dysuria. Complication-note the complications if any, occur after ozone therapy like pain at injection site, hematuria, perianal rashes, per rectal bleed.

DRE and PSA was done in all patients and patients who are having any evidence of Ca prostate were excluded. Patients who failed with IPOI were subjected to TURP and histopathological changes were evaluated with a pathologist.

Material required -Medical grade ozone generator for ozone production (water house company),One 22 French spinal needle ,One 20ml Syringe, One pair of disposable gloves. ,A lubricating jelly.

RESULTS

This prospective observational study was done in 50 patients. In all patients 40ml of ozone was instilled, maximum 3 times. Maximum number of patients were in the age group 61-70 years with the frequency being the most common symptoms. Out of 50 patients, 13(26%) patients had associated co-morbidities like hypertension, diabetes, COPD. All patients had an uneventful post ozone therapy course with mild pain at injection site (n=8), perianal rash(n=3), hematuria(n=3) and per rectal bleed in 1 patient which subsided within 24 hours.

Ultrasound was done in all patients before ozone therapy. Prostatic volume of all patients was assessed which ranges from 32 to 84 with the mean prostatic volume was 54.46cc.

Size of prostate was assessed after 1 week of IPOI with USG. After the 1st dose 23(46%) patients showed reduction in the volume of prostate, 25(50%) patients showed no change in the volume and 1(2%) patient lost to follow-up. After the 2nd dose 27(54%) patients reduced prostate volume, 15 (30%) patients showed no change in volume and 6(12%) patients lost to follow-up. After the 3rd dose 30 (60%) patients showed reduction in prostate volume, 10(20%) patients showed no change in volume and 8(16%) patients lost to follow-up [table1].

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Table 1: Effect of Ozone On Prostate Volume

Effect of IPOI on PV in no of cases	After 1st dose	%	After 2nd dose	%	After 3rd dose	%
PV reduced	23	46	23+4=27	54	27+3=30	60
Increase PV	1	2	2	4	2	4
No effect	25	50	15	30	10	20
Lost in follow up	1	2	6	12	8	16
Total	50	100	50	100	50	100

Mean prostate volume after 1st, 2nd and 3rd dose are 53.9cc, 53.69cc and 52.75cc respectively. Mean prostate volume reduction more after the 3rd dose [table2]. There was significant reduction in prostate volume after 3 weeks duration (p=0.0005).

Table 2: Prostate Volume Assessment (By USG)

Statistics	PV	PV post ozone		
	pre ozone	After the 1st dose. After the 2nd dose. After 3rd dose		
Mean	54.46	53.9	53.69	52.75
Std deviation	12.67	13.11	13.35	13.9
Minimum	32	28	28	30
Maximum	84	82	80	78
N	50	49	35	32

The mean prostate volume reduction was significantly more in successful voiders (void with uroflow rate of at least 10 ml/min) (mean=6.64) as compared to non voiders (mean=3.19). (P<0.0001) [table3].

Table 3: Prostate Volume Reduction Between Voiders and Non-Voiders

Improvement	Cases voided	Cases not voided
Mean PV reduction	6.64	3.19
SD	2.13	3.13
No of cases	14	28

Only 5(10%) patients underwent TURP after ozone therapy. Prostate volume reduction and satisfactorily(P<0.0001), voiding was seen in more patients in the current study as compared to previous study in which only a single dose of ozone therapy was administered.

DISCUSSION

Vitoria hypotheses that the increase in benign size of prostate, is due to an accumulation of metabolites or free radicals in the stroma which maintain a "latent" inflammation state as much of the stroma as of cellular epithelium, the action of ozone liquifying these metabolites would be beneficial. At the same time, ozone through the mechanism of ozonolysis at the membrane level increases the synthesis of PG's from type 2 arachidonic acid through the cyclooxygenases which would facilitate the mediating effect of the influence of hormones on these tissues. Just as the liberation of cytokines would promote the activation of the immune system. All of which would, as a whole, facilitate reduction and avoid blockages at the time of micturition.[1] The advantage of our study is inclusion of more patients as compared to study conducted by Vitoria et al, which was published in International Journal of Ozone Therapy, which was done on 9 patients. There is another study on Intraprostatic ozone therapy: a minimally invasive approach in benign prostatic hyperplasia published in Urology Annals in 2017.[2] Our study included 50 patients, which is significantly higher than the studies conducted previously, so the results will be more statistically significant.In this study ozone was injected per rectally under finger guidance as compared to Vitoria et al who blindly injected ozone through perineal. In our study fixed concentration (30 ug/dl) and amount (40ml) of ozone was injected as compared to study conducted by Vitoria et al in which variable concentration (30-40 ug/dl) and amount was injected, according to oxidative stress level of the patients. As our study had fixed protocol, so results are comparable, unlike the previously conducted studies which didn't mentioned any fixed protocols. Most of the patients fall in 61-70 age group (50%). Our study shows the same compared groups. Vitoria et al in his study had shown average age 41 years which is slightly lower as compared to our study. 36% of those patients had symptom duration more than 1 year and 64% of patients had symptom duration less than 1 year, as compared to study by Vitoria et al in which symptom duration was 3.1 years. We also included digital rectal examination, in which grade II prostate was found in 72% of patients while 28% patients had grade III prostate. In this study on 50 patients, acute urinary retention was noted in 100% of the subjects. 42% of them had associated increased frequency of urination while 16% had increased frequency associated with nocturia, 14% of the patients had associated increased frequency and urgency. In a previous study which was done on 30 patients, acute urinary retention was noted in 100% patients, 40% of them associated with increase in

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frequency of urination, 16.7% associated with increased frequency with nocturia, another 16.7% associated with increased frequency with urgency. While a study conducted by Vitoria et al had post void dribbling as the most common complaint followed by increased frequency and nocturia. In this study 26% patients associated with different co-morbidities like hypertension, diabetes, COPD. In a previous study 26.7% of patients had associated co-morbidities. In this study 18% of patients got relieved from urinary retention and 10% of patients had shown relief from retention and dysuria both where as in study conducted by Vitoria et al in which 33% (3 out of 9) of the patients got relieved post void dribbling. In previous study 13.3% of patients got relieved from urinary retention and 3.3% of patients had shown relief from retention and dysuria both.In this study 28% patients satisfactorily voided after ozone therapy who were previously catheterized for acute retention of urine as compared to previous study in which 16.6% patients voided satisfactorily after ozone therapy.In this study prostatic volume reduction on USG was noted in 46% after 1 week of 1st dose of ozone therapy, in 54% patients after 2nd dose and in 60% patients after 3rd dose. After the 1st dose of ozone therapy the mean reduction in prostate volume was 1.09cc, after the 2nd dose was 1.68cc and after 3rd dose was 3.18cc. More prostate volume reduction was noticed after the 3rd dose. In previous study prostatic volume reduction was seen in 40% patients after 7 days and in 56.7% patients after 1 month of the ozone therapy. In this study the mean prostatic volume reduction seen in patients who voided after ozone therapy were 6.64cc as compare to patients who didn't voided were 3.19cc. Similar results were seen in previous study i.e. mean prostatic volume reduction was more in voiders as compared to non-voiders. In this study 16% of patients had pain at local injection site, 8% of patients had perianal rashes which subsided after a course of antibiotics, analgesics, antiallergic medications, 6% of patients had hematuria and 2% of patients had per rectal bleed both were subsided spontaneously. In a previous study 16.7% of patients had local pain at injection site while 6.7% patients had perianal rashes. In this study 10% of patients who had no improvement after ozone therapy had to undergo TURP. In a previous study 13.3% of patients had undergone TURP. Effect of ozone therapy was more after 3 doses as compared to single dose of intra prostatic ozone injection. No specific histopathological change was seen in patients who had undergone TURP after ozone therapy.

CONCLUSION

This prospective study was done in NSCB Medical College, Jabalpur, from March 2017 to August 2018. We assessed the effect of ozone therapy in benign prostatic hyperplasia patients by performing intra prostatic ozone injection in 50 patients of median age 64.5 years, mostly of grade II and III prostate, (on DRE and USG) who was failed TWOC (trial without catheter) after alpha blocker trial. In these patients 40ml of ozone at 30 ug/dl concentration was injected in both lateral lobes (20ml in each lobe), through 22 fr spinal needle by finger guidance. Total 3 doses of intraprostatic ozone injection was given at the interval of one week. 18% of patients got relief from urinary retention and 10% of patients had shown relief from retention and dysuria both. After 1 week of 1st, 2nd, 3rd dose ozone therapy prostatic volume reduction are 46%, 54% and 60% respectively. The mean prostatic size reduction in terms of prostatic volume was 1.04cc, 1.68cc, and 3.14cc after 1 week of 1st, 2nd and 3rd dose of ozone therapy respectively. Most of the prostatic volume reduction was noticed in the 1 week to 3 week period. In our study 28% patients voided satisfactorily after ozone therapy who were previously catheterized for acute retention of urine. The mean prostatic volume reduction seen in patients who voided after ozone therapy as compared to patients who didn't voided were 6.64 and 2.61 respectively. There were no major complications related to ozone therapy and fewer patients (10%) went for TURP. Intraprostatic ozone injection helps to reduce the prostate size to some extent. Intraprostatic ozone injection can be helpful in some patients who have failed trial without catheter even on alpha blockers and are unfit for TURP.This is a minimally invasive procedure which can be performed easily without any major complications. This is cost effective therapy. This procedure can be included in minimal invasive procedures for BPH and can be useful in some patients where standard treatment cannot be contemplated. Larger studies are required to assess efficacy and long term results of this technique. This procedure especially can be helpful in patients with different co-morbid conditions and TURP is not possible.

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