Original Article

Effects of Drugs on Prostatic Hyperplasia

Comparative Study of Clinical Outcomes of Monotherapy and Combination Regime of Doxazosin, Finasteride on Benign Prostatic Hyperplasia in Pakistani Citizens

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ABSTRACT

Objective: To investigate better clinical success with combination regime of doxazosin, finasteride or when either of the two drugs used as monotherapy on benign prostatic hyperplasia.

Study Design: Descriptive / cross sectional study.

Place and Duration of Study: This study was conducted at the DHQ Hospital Sahiwal & Ghulam Muhammad Mahar Medical College & Teaching Hospital Sukkur from January 2014 to March 2016.

Materials and Methods: This descriptive cross sectional study was done on 3000 patients with symptomatic BPH (benign prostatic hyperplasia). Amongst them, initial 100 patients were recruited for pilot study and 2900 patients were involved in the full-scale study. Total number of patients was divided into four groups, placebo, patients taking doxazosin, monothery with finasteride, combination therapy group. Medication was classed into two groups; first group drugs with potential clinical benefits, second group comprised 'placebo' drugs, mimicked shape wise and taste similar to doxazosin or finasteride.

Results: After a follow up 1 to 3 years, in all men of more than fifty years coming with signs and symtoms specific for BPH where surgery was not the consideration, the highest incidence of successful clinical outcomes were noted with patients taking combination regime of Doxazosin, Finasteride on benign prostatic hyperplasia.

Conclusion: Successful clinical outcomes were achieved in our research work when combination regime of Doxazosin, Finasteride on benign prostatic hyperplasia were used, rather than when either of the two drugs were used as monotherapy

Key Words: Doxazosin, Finasteride, Benign prostatic hyperplasia

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INTRODUCTION

In old age, one of the very important causes of complications of lower urinary tract is benign prostatic hyperplasia (BPH).[1] The quality and mode of life is badly influenced by these complications. These complications may include the recurrent UTIs, the blockage of the urethral pathway, the incontinence and retention of urine, or maybe a need of surgical interventions.[2]

The alpha blockers are usually given to such patients with symptomatic hyperplasia of prostate gland, as they act on alpha adrenergic receptors present on prostate and antagonizes them hence decreases the tone of bladder neck and smooth muscles present in prostate.[3] The other drug class given in such cases is 5α-reductase inhibitor (5-ARIs), which inhibits the 5 alpha reductase enzymes and which has antiandrogenic nature as they inhibits the conversion of testosterone to dihydrotesto-sterons and decreasing the prostate volume by causing the atrophy of prostate epithelium. Variety of modalities of applied research proved the benefits of alphablockers to facilitate the better clinical outcomes and facilitating the passage of urine out of the urinary tract.[4] Literature survey reveals research work of 48 months duration states that BPH considering its clinical follow-up, patients continue to complain frequency of urine, urgency of urine, urinary tract infections and at times obstruction to the flow of urine.[5,6] Patients may end up complaining the obstruction to the normal flow of urine, or may require surgical interventions. The 5a reductase inhibitor (finasterides) decreases the possibility of complications of benign prostatic hyperplasia. It has been proved by another research that when 2 drugs are administered to the patient , the relief of symptoms regarding improvement in the clinical

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symptoms were just similar to when only one drug was given to the patient.[7,8] Two terminologies are synonymous namely, benign prostatic hyperplasia and benign enlargement of prostate. It must be noted here that this increase in gland is not actually the carcinoma of the gland but an increase in size of gland due to the increase of the gland's parenchyma and connective tissue cells that leads to increase in size of the prostatic discrete collection of cells which results in alteration in normal anatomical architecture of the gland featured by collection of cells as compact discrete masses within the normal domains of the gland.[9] This all leads to the enlargement of all lobes of the gland in general and median lobe enlargement in particular. This causes pressure symptoms to the prostatic urethra precipitating the local urinary tract infection and obstruction to the flow of urine which is troublesome to the patient.[7,8] Though obstruction is misnomer here as the intra urethral diameter is transiently compromised. When there is obstruction to the urethra, the first outcome is the over excertion of the detrusor muscle of bladder wall, micturition becomes troublesome, the clinical setting is progressive meriting conservative management and surgery is the last resort.[9] It must be noted here that benign prostate hyperplasia is actually the increase in the number of cells and not the increase in size of the cell. The level of PSA may gets elevate due the hyperplasia of the gland or maybe due the infection in the gland, BPH is a benign condition, this is as they say when the hair turn grey, when the wrinkles come on the face, this is the age for prostate gland and this is the normal component of aging scenario in men, When there is increase in parenchymal cells in any lobe of the gland and this is common in age group of over 50 years.[10] in diabetic patients lesser age groups ie lesser that 40 years of age may get this clinical. Secretions of prostate gland are liquid form and become component of semen. Patients complained nocturnal frequency that they had repeated desire at bed time to micturate. Clinical presentation of the patient also involved painful and troublesome micturition, patients experiencing drops of blood continued passing through urethra.[11] Actually management of benign prostatic hyperplasia should only be considered when start complaining of moderate to severe specific clinical picture of this problem. Benign prostatic hyperplasia can be managed conservatively and then operative option is also there. The prostate gland is present around the urethra in the area just under the bladder. It is a very tiny organ present only in men which makes a fluid that helps to nourish sperm as part of the semen. Treatment results in successful decrease in symptoms in majority of people without affecting the sex drive of the person. Best clinical method to diagnose benign prostatic hyperplasia is through digital approach per rectum and a very relevant investigation is by applying a cytoscope.[12]

MATERIALS AND METHODS

This descriptive cross sectional study was done on 3000 patients in DHQ Hospital Sahiwal & Ghulam Muhammad Mahar Medical College & Teaching Hospital Sukkur from January 2014 to March 2016. Amongst them, initial 100 patients were recruited for pilot study in which follow up was maintained till two years and 2900 patients were involved in the full-scale study where follow up was done for four years. Total number of patients was divided into four groups, placebo, patients taking doxazosin, monotherapy with finasteride, combination therapy group. Medication was classed into two groups, first group drugs with potential clinical benefits, second group comprised 'placebo' drugs, mimicked shape-wise and taste similar to doxazosin or finasteride.

All patients gave written informed consent. Patients irrespective of their age, sex, past history of BPH signs and symtoms were involved in this study. The patients of more than 50 years of age with classic BPH symptoms score were admitted through out patients departments. Demographical variables included age, name and sex of each patient and complaints presented by the patients. We did not include in current research work the patients with severe pathological deformities, cases who had surgery on prostate or this gland was treated conservatively, and those with unclear documents Exclusion criteria from study included patients having previous abdominal surgery, very low blood pressure, bleeding diathesis and the patients not fit for general anaesthesia. All those patients having elevated serum PSA (prostate-specific antigen) level of greater than 10-12 ng per milliliter.

Total number of patients were divided into four groups, placebo, patients taking doxazosin, monothery with finasteride, combination therapy group. Medication was classed into two groups, first medications producing clinical effects, second placebo drugs, later group included tablets which were shape-wise and taste wise mimicking doxazosin and finasteride. We planned different treatment regimes in different hospitals. Patients were advised to have drugs only at night times. As a policy finasteride was regularly administered 5 mg daily. Different schedule was planned for doxazosin, as it was given double the dose daily routinely at one-week intervals, it started as 1 mg once in 24 hours till seven days, this plan continued till we achieved the target of final daily dose of 8 mg. Significant side effects appeared in fifteen patients, we changed treatment regime to 4-mg instead of 8mg, nine patients did not even tolerate 4mg. Total of five patients who developed adverse side effects with 8mg or a 4mg dose were labeled as non compliance group of patients, they stopped taking doxazosin.

Blood pressure, pulse rate, respiratory rate, heart rate charts were maintained, also intensity of signs and

symtoms of benign prostatic hypertrophy was obsereved, maximal urinary flow rate record was also maintained for a period of 3 months, directly observed therapy plan was also exercised which included patients tolerability to medication and side effects were also noted for a period of ninety days. P/R, assessment of prostate specific antigen, complete urine tests were on yearly basis.

The continues retention of urine , the kidney problems , the UTIs, or discontinuation of urine outflow were declared as primary outcome. In situations when patients could not micturate having obstructed outflow, we labeled them as acute urinary retention**.** BPH is underlying cause of kidney failure and is diagnosed when anorexia, nausea, vomiting fatigue, lethargy with urinary symtoms, serum creatinine 1.5 mg per deciliter. When more than two events of infections involving any part of urinary tract in a period of one year occure, we label it as recurrent urinary tract infection. Unintentional, uncontrolled bed wetting causing a lot of cleanliness issues, for which patient himself feels guilty, visits doctor and tells this symptom as first complaint of his clinical presentation. We had formulated a board of doctors for exact follow up of these all patients, particularly the complaints of the patients, but importantly these board members did not know which medications were being administered to the patients. Late follow up changes in clinical presentations, like sudden inability to micturate, kidney function impairment, repeated infections of urine outflow tract, automatic unintentional voiding, also maximum micturition flow rate were labeled as secondary follow up changes.

RESULTS

After a follow up 1 to 3 years, in all men of more than fifty years coming with signs and symtoms specific for BPH where surgery was not the consideration, the highest incidence of successful clinical outcomes were noted with patients taking combination regime of doxazosin, finasteride on benign prostatic hyperplasia. Total of three hundred and fifteen primary outcome events appeared, Maximumm number of such events were observed, as 114 (placebo group), 81 (doxazosin group), 85 (finasteride group), and 43 (combination-therapy group). Blood pressure, pulse rate, respiratory rate, heart rate fluctuations were observed, also intensity of signs and symtoms of benign prostatic hypertrophy was found distressing 114 in the placebo group. The continues retention of urine, the kidney problems, the UTIs, or discontinuation of urine outflow declared as primary outcome were found in moderate to severe intensity placebo group.

Acute obstruction to urinary outflow, kidney impairment in moderate forms were documented in eighty one patients in the doxazosin group. Blood pressure, pulse rate, respiratory rate, heart rate fluctuations were not depicted in this group. Anorexia, nausea, vomiting fatigue, lethargy with urinary symtoms, serum creatinine 1.5 mg per deciliter was present 85 in the finasteride group. Recurrent urinary tract infection, unintentional, uncontrolled bed wetting, causing a lot of cleanliness issues and moderate to severe intensity of signs and symptoms of benign prostatic hypertrophy like acute obstruction to urinary outflow, kidney impairment, blood pressure, pulse rate, respiratory rate, heart rate fluctuations were observed troublesome in only forty three patients in the combination-therapy group. Board of doctors for exact follow up of these all patients, particularly the complaints of the patients, but importantly these board members did not know which medications were being administered to the patients.

DISCUSSION

Standard living conditions of aging patients may be influenced by BPH and by infection of ureter, urinary bladder and urethra.[13]. The BPH leads to constant retention of urine, the kidney problems, the UTIs, or discontinuation of urinary outflow along with some other complications .The use of different drugs like doxazosin and finasteride help to decrease the symptoms and and help to normalize the urinary outflow. The need of surgical interventions is minimized with the use of finasteride which decrease the size of the gland.[14]

Two years researches were made out for this purpose that included the combined treatment and use of alpha blockers and 5α reductase inhibitors. The VAC studied the effect of finasteride, the alpha blocker (terazosin), combined therapy of two with placebo while the other research studied the effect of finasteride, alpha blocker (doxazosin), combined therapy of both with placebo.[15-17] The result of the researches were that the combined therapy was not that useful as compared to the individual drug used but the research showed that there is a definite decrease in the BPH complications and clearance in outflow of urine.[18,19]

The result showed that there is a decrease in all the symptoms of BPH with the use of finasteride, alpha blockers (doxazosin) and the combined use of two but the combined treatment with the two showed the maximal result as compared to the individual drug used alone.[20]

From the parts of the composite primary outcome, a confirmed increase from base line in the benign prostatic hyperplasia complications score of at least four points was reoccurring event. This result has clinical importance, as in people with BPH many complications are the cause for invasive therapy.[21] In a 1 year research the mean increase of the BPH clinical picture and aging men take it as a serious medical and social issue.[22] The combined treatment was more useful

and fruitful in reducing the symptoms as compared to the individual drugs used alone.[23]

As a result of research we came to know that when 5α-reducatse inhibitor (finasteride) and combined therapy were given, both showed the similar result in preventing the need of surgical interventions and in retention of urine of acute nature.[24,25] Monotherapy with doxazosin brought about postponing in acute retention of urine and also in delaying the need of surgery, these patients did experience acute urinary retention and surgical intervention later in course of current research work.. So major benefit of treatment with doxazosin alone lessened incidence of acute urinary which is main work of alpha-blocker which bring about relaxation of smooth-muscle tone present in prostate gland.[26]

Comparatively, if we can achieve the target of getting tomography of prostate gland to lesser dimensions, the chances of sudden blockage of urinary outflow and surgical interventions during the period of current research work, are reduced. Operative technique in not the ultimate option of managing acute urinary obstruction. Voiding trial remains a thoughtful entity, its success depends upon time and various factors causing urinary out flow obstruction events. In the indexed literature, it has been documented in the placebo category done in 4-year research work 17% of patients developed urinary obstruction during follow up when desired results were achieved in voiding trial and 75% needed operative work.[27] An insight into literature depicts 29% patients within placebo category got desired results of voiding trial post acute urinary obstruction event.[28]

Importantly results of current research work show urinary tract infection are very uncommon, which indicate that urinary tract symptoms and BPH do not have strong clinical relevance. Another finding in our current study is that kidney failure is not likely to occur even if BPH is left unmanaged actively at least during our trial. Indexed literature states clinical testing assessing how much alpha-blockers and combination treatment are effective were of very short duration of lesser than 12 months.[29,30] It is pertinent to mention that our research work is of much longer duration and results are comparable to those researchers who did study in past. So we claim the longer duration effectiveness of doxazosin, finasteride, and combination treatmen. A survey in indexed literature done on three thousands patients who were administered either finasteride or placebo. That research work was of 4 years duration in which a couple of patients reported with growth in mammary gland seen in placebo group and not a single patient got it in the finasteride category of patients. In yet another documentation regarding prostate prevention conducted on eighteen thousands patients who were casually selected to be administered 5α-reductase inhibitor (finasteride) or placebo, found similar incidence of documented patients of growth in mammary gland in 5 years observation.

In the two studies ie alpha blockers group (doxazosin) and placebo group the overall size of prostate, the serum prostate specific antigens count, the outflow rate of urine and the seriousness of symptoms showed the chances of increase in benign hyperplasia of prostate and the use of surgical interventions by percentage ranging from 0.59%-5.63%. But in case of therapy which included the use of these drugs in a combined form, these complications do not show any type of progress in the disease and only prostate specific antigens count suggests the chances of surgery or retention of urine. The hyperplasia and growth of the prostate is directly linked to the prostate specific antigens level, the increase in growth leads to increase in level which is helpful in predicting whether the disease is regressing or worsening.

There is no clear cut linkage in the group with combined therapy among the chance of progress and the level of prostate specific antigens which was a proof that the treatment is going fine and results are favorable however the chance of worsening of the disease in people in placebo was less for the people with the less level of prostate specific antigens. Total number of patients were divided into four groups, placebo, patients taking doxazosin, monothery with finasteride, combination therapy group. Medication was classed as two groups, first potential action producing medication and second placebo drugs, which were shape wise and taste wise resembled like doxazosin or finasteride.

Current research work has documented that combined treatment with doxazosin and finasteride lowered danger of severity of signs and symptoms of BPH more than when either drug given alone. Also chances of acute urinary blockage and indication for operative work for BPH were lowered with combined treatment. Desirable clinical outcomes regarding maximal urinary flow rate were also noted so combined treatment is appropriate and precisely indicated for patients of BPH having lower urinary tract symptoms, more over patients showed reduced danger of increasing severity of symptoms.

CONCLUSION

Successful clinical outcomes were achieved in our research work when combination regime of doxazosin, Finasteride on benign prostatic hyperplasia was used rather than when either of the two drugs were used as monotherapy. Combined treatment is most appropriate and highly indicated for conservative management of BPH where survey is not the option.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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