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Original Article

Synergistic Effect of Curcumin on Controlling Irritative Urinary Symptoms After Benign Prostatic Enlargement Endoscopic Surgery Compared with Anticholinergic Therapy Alone

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HIGHLIGHTS

- This study was one of the first randomized clinical trials to investigate the effect of curcumin on controlling urinary symptoms in patients with benign prostatic enlargement who underwent endoscopic surgery.
- This study was one of the first to evaluate curcumin's effects on reducing symptoms of benign prostatic hyperplasia as a randomized clinical trial. The results showed that curcumin had a positive effect on decreasing these symptoms, although changes in nocturia were not significant.

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ABSTRACT

Introduction
Benign prostatic hyperplasia is a common condition in older males that causes bothersome symptoms. The purpose of this study is to evaluate the combined impact of curcumin and anticholinergic therapy in managing urinary irritation symptoms in patients with benign prostatic hyperplasia following prostate surgery.

Methods
This randomized clinical trial included patients with benign prostate hyperplasia who experienced irritating symptoms after prostate surgery at Imam Reza Hospital in Mashhad from 2019–2020. Participants completed the IPSS questionnaire before the operation and were then classified into two groups. One group received anticholinergic therapy, and the other group received anticholinergic therapy plus curcumin BID for one month. The IPSS was used again at the end of one month, and results were analyzed using SPSS statistical software.

Results
80 participants were included in this research, with an average age of 63.4±13.5 years in the control group and 64.6±9.5 years in the intervention group. Before the intervention, scores for urinary frequency (P-value=0.333), urinary urgency (P-value=0.387), nocturia (P-value=0.807), and total urinary symptom score (P-value=0.061) differed between the two groups. However, after the study, the intervention group had significantly lower scores for urinary frequency, urinary urgency, and total urinary symptom score compared to the control group (P-value<0.05). No significant difference was between two groups considering nocturia (P-value=0.051).

Conclusions
This investigation was one of the first randomized clinical trials to evaluate curcumin's effects on reducing symptoms of benign prostatic hyperplasia. The results indicated that curcumin positively impacted decreasing these symptoms, although changes in nocturia were not significant.

Keywords: Benign Prostatic Hyperplasia; Curcumin; Lower Urinary Tract Symptoms; Alpha-Blockers; 5-Alphareductase Inhibitors

Introduction

Benign prostatic hyperplasia (BPH) is defined as an age-connected progressive condition of the urinary system occurring among middle-aged males (1). Histologically, BPH is described by the enlargement of the prostatic epithelium as well as the stromal cells of the prostate cells (2-4). Biochemically, it is believed that an imbalance among androgen and estrogen levels, as well as the overexpression of growth factors, results in BPH (3, 5, 6). Previous research has proved that half of older men over 50 years of age suffer from BPH (7-10). Inflammation of the prostate plays a momentous role in the progression and pathogenesis of BPH (11). BPH dramatically affects the quality of life of approximately 70% of men over 80 years of age (12) and commonly causes lower urinary tract symptoms (LUTS) (1, 4, 13). Representing moderate-to-severe obstructive and irritative symptoms (14). LUTS can cause different complaints, such as needing to urinate recurrently, difficulty in voiding, weak urine stream, urgency, frequency, straining, the inability to urinate, nocturia, or loss of control over bladder function (15-17). This may increase the susceptibility to urethral obstruction, urinary retention, bladder stones, hematuria, recurring urinary tract infections, and even renal failure (2, 18-21).

The diagnosis depends on the clinical background, and complementary examinations are highly valuable to determine the level of obstruction and eliminate other complications and other alternative diagnoses (21). The management of symptomatic BPH is commonly multimodal (22-24).

Modern science advocates medical as well as surgical approaches (12). Treatment of BPH includes the a1-adrenergic receptor antagonists (such as tamsulosin), which alleviate LUTS by expanding smooth muscle in the prostate gland as well as the bladder neck, and the 5a-reductase inhibitors. Both of them lack anti-inflammatory impacts and have probable side effects. While these drugs have been proven to be efficient in the cure of BPH, (25). When pharmacological management loses efficacy, surgical intervention becomes necessary (26). Over the last two decades, there has been a rise in minimally invasive techniques for the treatment of BPH, such as laser and plasma enucleation or laser and plasma vaporization (27). Although transurethral resection of the prostate (TURP) is known as the gold standard treatment for BPH (28), it is not far from adverse effects (17, 23, 26).

Bladder spasms and burning sensations during urination are the most prevalent side effects of surgery that can be cured by the prescription of drugs. Management of BPH always includes the prescription of NSAIDs as well as anticolinergics. The utilization of NSAIDs and anticolinergics can result in different side effects, such as non-specific colitis as well as large intestinal ulcers, bleeding and perforation, inflammatory bowel disorder, inflammation of the small intestine, and protein loss (29). Frequent consumption of NSAIDs can result in complications such as Presence of other complications such as heartburn, diarrhea, vomiting, and nausea that are challenging (28).

Current therapy for BPH induces a wide range of different side effects. Some bioactive agents from natural sources have been potentially proposed to cure different side effects (30).

Currently, the potential healing properties of medicinal herbs as traditional medicines have attracted a great deal of attention in urology (31).

Curcumin (CUR) is a polyphenolic pigment of the perennial herb turmeric (Curcuma longa) (32) that has a pleiotropic effect on many targets like immunomodulatory, anti-inflammatory, and natural antioxidant pathways (33). CUR affects the inflammatory response by down-regulating the inflammatory pathways (34), inhibiting the release of inflammatory biomolecules and decreasing the release of proinflammatory cytokines (35). There is multiple evidence and different research done that proves the potential therapeutic impact of CUR (34).

In the current study, we highlighted the impact of combining herbal medicine with conventional therapy for BPH. The major purpose of our investigation was to estimate the effectiveness of CUR in managing postoperative complications such as burning urination and bladder spasms, as well as reduce bladder irritation, as an alternative treatment that may effectively replace NSAIDs as well as anticolinergics.

Methods

Study Design

This single-center, randomized clinical trial was designed to evaluate the efficacy of CUR in the elimination of post-TURP syndromes. This trial was recorded in the Iranian Registry of Clinical Trials (IRCT20170417033489N9 on January 20, 2021; obtainable at: https://www.irct.ir). The Ethics Committee of Mashhad University of Medical Sciences approved this study (IR.MUMS.MEDICAL.REC.1399.630), and all patients signed the informed consent. This study includes elderly men with a diagnosis of LUTS secondary to BPH (BPH/LUTS) who need surgery for TURP. All patients who reported moderate to severe LUTS secondary to TURP were referred to the outpatient urology clinic of the EmamReza Hospital of Mashhad between February 2019 and May 2021. This randomized clinical trial was performed by selecting patients among those who underwent TURP. In the first postoperative visit, 80 patients who suffered from LUTS after TURP were enrolled in our research based on the inclusion criteria. Next, they filled out informed consent. Afterward, a special questionnaire was filled out to gather different parameters of LUTS. Patients were

randomly divided into two separate groups based on their treatment plans. Those in the first group were suggested to take anticholinergics and NSAIDs, while patients in the second group were prescribed anticholinergics and NSAIDs as well as an additional herb-drug, CUR, in the form of a tablet and at a dosage of 80 mg two times per day. Patients were revisited after one month. Between the initial postoperative visit and the last visit as a follow-up, a questionnaire was filled out to compare the different parameters of LUTS. Data were gathered by the IPSS questionnaire.

Inclusion and exclusion criteria

The inclusion criteria were the presence of symptoms of LUTS associated with TURP. All patients with the presence of LUTS before surgery were excluded. Men with fever and prostatitis symptoms were also excluded. The participants with active UTI (clinical symptoms related to UTI with a positive culture) were excluded.

Intervention

Participants were randomly allocated to the CUR group which took CUR+ anticholinergics and NSAIDs (n=40) and the BMS (the best standard management) group (n=40) which took only anticholinergics and NSAIDs. Each CUR tablet contained 80mg of CUR. The CUR and BMS groups were labeled as “code A” or “code B." The Pharmacy Department of Mashhad University was randomized and blinded. Afterward, the qualified participants were assigned randomly to either "code A or B" for their groups. The codings were sent to the main researcher through mail once the follow-up and final analysis were completed. For the duration of the study, participants were given clear instructions to take two tablets per day. This routine was to be followed for 30 days, starting with the presence of postoperative LUTS. To encourage cooperation, we utilize telephone and text messages to remind each participant about the timing of drug consumption (36).

Diagnosis of LUTS

The IPSS questionnaire is a 7-item self-expression urinary symptoms scale for measuring the severity of some symptoms presenting over the previous month (24). It was filled during initial assessments and subsequent follow-up examinations. It can be used to determine the severity of different parameters, and one single item is correlated with the patient’s quality of life (37). The IPSS, a modified version of the American Urological Association Symptom Index, underwent validation almost three decades ago to evaluate males with BPH (24). After assigning a score to each item, the values are added together to calculate the severity of the symptoms. The rating scale ranges from 0 to 35, with a score of 0 indicating "none" and a score of 7 referring to "severe" (24). Patients were given instructions to select a single numerical option for each question, resulting in an overall score that could range from 0 to 35. The World Health Organization has recommended the use of this method in randomized clinical trials aimed at treating LUTS (38). This approach has been widely employed and tested in various therapeutic studies (39).

Statistical analysis

Statistical analysis

Statistical analysis was performed using SPSS statistical software version 20.0. All results are described as continuous variables with a mean ± standard deviation (SD), as well as categorical variables such as frequencies and percentages. The data were analyzed statistically by the Student’s T-test. Furthermore, intergroup and intragroup changes in clinical indicators were assessed by the Student’s T-test and chi-square test. All statistical analyses were two-sided as well as considered significant at P-value<0.05.

Results

Patient characteristics

A total of eighty men were included in the trial who had complaints of LUTS after TURP. Patients were allocated into two treatment groups. The mean age in BSM group was 63.4±13.5 years, with a median age of 64.6+9.5 years in CUR group. No statistically significant difference was between age in two groups (P-value=0.458). Before the intervention, the scores of patients regarding frequency (P-value=0.333), urgency (P-value=0.387), nocturia (P-value=0.807), and total disease symptoms (P-value=0.06) were not significantly different between the two groups. Records were statistically analyzed using Student’s T-test. Several characteristics of clinical indicators studied are demonstrated in Table 1 and Figure 1.

At the end of the 1-month treatment, the scores of patients regarding frequency, urgency, nocturia, and total scores before and after the intervention decreased significantly (P-value>0.05). The results are illustrated in Table 2.

The results of the comparison between two groups after intervention are shown in Figure 2. In the intervention group, the scores of patients regarding frequency, urgency, and total scores decreased significantly compared to control group (P-value=0.001). Although changes in the nocturia parameter were not significant in two groups (P-value=0.05).

Discussion

In this paper, we studied a 1-month follow-up therapy to assess the efficacy of a mixed treatment of anticholinergic drugs plus CUR for 40 patients suffering from LUTS/ BPH in comparison to 40 patients on anticholinergic and

Table 1. Between-group comparisons of clinical parameter groups before intervention

CharacteristicS		Patient's score		P-Value
		SD	Mean	
Frequency	Control Group	1.15	3.70	0.333
	Intervention Group	1.35	3.42	
Urgency	Control Group	1.04	3.80	0.387
	Intervention Group	1.25	3.57	
Noctuary	Control Group	0.46	0.20	0.807
	Intervention Group	0.44	0.17	
Overall score IPSS	Control Group	1.13	7.70	0.061
	Intervention Group	1.83	7.05	

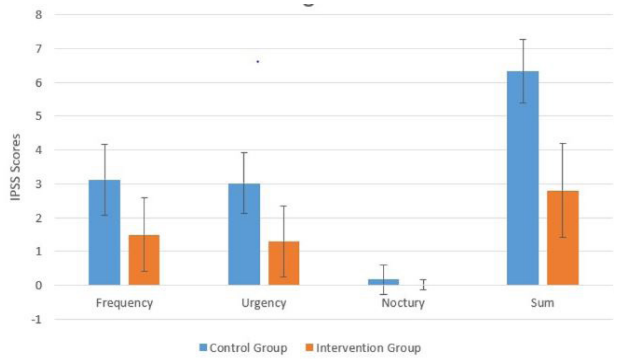

Figure 1. Between-group comparisons of clinical parameter groups before intervention

Table 2. Comparisons of the control group before and after the intervention

Characteristics		Patient's score		P-Value
		SD	Mean	
Frequency	Before Intervention	1.15	3.70	>0.001
	After Intervention	1.35	3.42	
Urgency	Before Intervention	1.04	3.80	>0.001
	After Intervention	1.25	3.57	
Noctuary	Before Intervention	0.46	0.20	0.32
	After Intervention	0.44	0.17	
Overall score IPSS	Before Intervention	1.13	7.70	>0.001
	After Intervention	1.83	7.05	

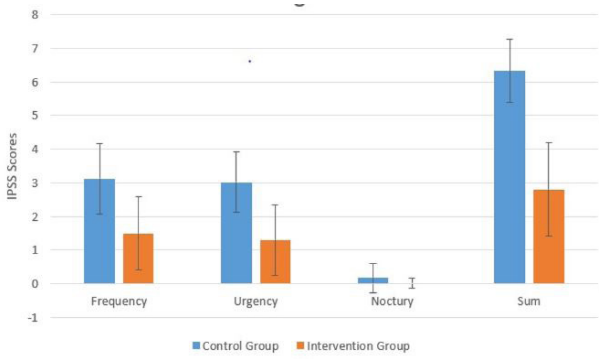

Figure 2. Comparisons of two groups after the intervention

NSAIDs alone. The frequency, urgency, and total scores of prostate symptoms in the group of mixed therapy and CUR were dramatically decreased compared to the anticholinergic group alone. Our findings show that patients' symptoms, including frequency, urgency, and total scores, dropped dramatically after 1 month of follow-up in the mixed conditional therapy and CUR groups, which was statistically significant in comparison to the control group. These results can be explained by the fact that CUR may function as a protective pharmacological drug in humans, too.

CUR, one member of the Zingiberaceae family, is a bioactive polyphenolic ingredient compound from Curcuma longa (40). CUR has a varied range of defensive pharmacologic effects, like anti-inflammatory, anti-neoplasmic, neuro- and cardio-protective, antioxidant, immunomodulatory, analgesic, lipid-lowering, and antidepressant properties. It is inexpensive and highly safe for humans (41-46).

CUR can interact with various molecular target pathways and modulate their activity, including enzymes, inflammatory cytokines, growth factors, transcription factors, receptors, hormones, and adipokines, as well as several signaling cascades (30, 46).

CUR is recognized as the key bioactive ingredient of turmeric (47), traditional medicine that was used as a herbal medicine more than 200 decades earlier in China and India with several health properties (48), like varied drug activities in contradiction to aging, including dermatologic changes (50), retinal disorders (51), Parkinson's disease (PD) (49), renal antioxidative effects (53), ischemic oxidative harms in different tissues (50-52) and malignancies (53). CUR analogs can ease the degradation of androgen receptor (AR) in prostate cancer (54) and might induce apoptosis of prostate cancer cells by IkBalpha, c-Jun, and androgen receptor (55). CUR proves a suppressive impact on HIF1a (56, 57), introduced as a main molecule for deformation from prostatitis to BPH (58). Furthermore, it was confirmed to be an effective TNF blocker (41), and its antioxidant influence can suppress LOX1 (59). Management of CUR was considered liposomal-formulated CUR in Parkinson's disease (PD) (49) and lecithinized CUR delivery system in BPH (35). The prior studies show that CUR could have a protective role in BPH, but the impact of CUR on BPH is not studied, known as responsible for the synthesis of DHT, which is an active metabolite of testosterone. So, we decided to assess if CUR has a protective effect on testosterone-induced BPH. Earlier experimental research has confirmed that CUR has anti-inflammatory, anti-

cancer, antioxidant, lipid-modifying, anti-fibrotic, and anti-arthritic effects.

Furthermore, CUR has been known to efficiently inhibit the development as well as the occurrence of BPH in male Wistar mice and decrease the expression of TGF-1 which is an inflammatory cytokine, in the prostate gland (60). Study illustrations CUR is a highly pleiotropic molecule capable of influencing several molecular targets involved in inflammation.

Ledda et al., (35) evaluated two plans according to a standard therapy [defined as the best standard management] including or not CUR (administered as Meriva®) as an adjuvant element. The research was done by a total of 61 participants. Meriva® was prescribed at a dose of 100 mg CUR. The results in the Meriva® group were listed as follows: Feeling of incomplete bladder emptying, urine frequency, urgency, intermittency, weak stream, strain, and nocturia was considerably lesser than the BSM-only group (P-value<0.05). No side effects were reported. The life quality upgraded in two groups, however, was dramatically improved in the Meriva® group (P-value<0.01). There was also a considerably more momentous reduction in subclinical and clinical episodes of urinary infections as well as urinary obstruction in the Meriva® group (P-value<0.01).

In a study done by Kim et al., (60) the rats with BPH were split into four groups as follows: (A) a normal group; (B) BPH due to intaking of testosterone by subcutaneous injection; (C) a CUR group that was treated with orally prescribed testosterone for 1 month; (D) finasteride group that was treated by injection of testosterone subcutaneously for 1 month. The recommended dose of CUR to take was 50 mg/kg, as mentioned in a prior study (41). Body weight change illustrations show that prostate volume, prostate weightiness, and prostate weight ratio in two groups of CUR and finasteride cure considerably declined in comparison to those of the BPH group (60). Compared to the finasteride group as a positive group, the CUR group revealed a similarly protective influence on BPH in morphology, histopathology, and prostate volume. Also, results of immunohistochemistry and western blot tests illustrated reduced expressions of VEGF, TGF-ß1, and IGF1 in CUR group.

Hejazi et al., (61) investigated the impact of CUR supplementation during radiotherapy on the oxidative status of participants with prostate carcinoma. Patients were assigned randomly to either the CUR group taking a dosage of 3 grams of CUR or the control group participants taking a placebo. The current research has approved that CUR can surge total antioxidant capability as well as reduce superoxide dismutase action in the patients's plasma during radiotherapy. Furthermore, levels of prostate-specific antigen (PSA) declined to below 0.2ng/ml in both groups 3 months later, though no momentous changes were detected among the 2 groups concerning treatment outcomes. The observations are considered effects of CUR as antioxidant properties.

Hejazi et al., (62) investigated the effects of CUR supplementation in prostate cancer patients. Forty patients with prostate cancer who underwent radiotherapy were accidentally allocated to the CUR group, taking 3g/d CUR, or the placebo group (n=20). Quality of life was measured through a prostate cancer-specific questionnaire (QLQ-PR25). An analysis of covariance was done for radiotherapy-related signs among groups after the intervention compared to baseline signs. No statistically significant were differences in bowel or urinary symptoms, treatment-related symptoms, or sexual activity between the CUR and placebo groups before the intervention. But, the variation in urinary symptoms during the 5 months differed dramatically between groups (P-value=0.011), and participants in the CUR group declared milder urinary symptoms in comparison to the placebo group. No differences were detected in any other domain of the QLQ-PR25. So, they proved that CUR can confer a radioprotective impact on participants with prostate cancer who underwent radiation treatment by decreasing the severity of radiotherapy-induced urinary symptoms. Though supplementation of 3 grams per day could decrease the severity of bowel and urinary symptoms, Cur is a strong and famous anti-oxidant and anti-inflammatory agent. The mechanisms responsible for the protective impact of CUR on the urinary system were not examined specifically in this study. Though several mechanisms have been suggested for the radioprotective influence of CUR, In in vivo research, it was proved that CUR confers its radioprotective effect by reducing gene expression of inflammatory (IL-1, IL-6, IL-18) and fibrogenic cytokines (TGFβ) (63).

BPH is a common disorder leading to lower urinary tract symptoms (LUTS) in elderly males (64). while the cause of LUTS due to BPH is not being recognized. Frequent research has recommended that BPH is a multifactorial disorder (65). Though it has been recognized that hormonal factors are related to the overgrowth of the prostate gland (64), in recent years, growing diverse facts show that BPH is linked to chronic inflammation (65, 66). Moreover, it has been proven that LUTS is correlated to BPH (67, 68). Administration of BPH contains medications, therapy, and surgery. Surgery is recommended for those who fail to cure or do not respond to drug treatment, which includes TURP, prostate laser vaporization, holmium laser resection of the prostate, etc. Although a surgical procedure has different adverse effects, like bleeding, retrograde ejaculation, urethral stenosis, and urinary incontinence (69, 70). Standard medical management for LUTS/BPH is anticholinergics and NSAIDs, both of which have potential adverse effects (71, 72).

BPH is a prevalent condition in aging males. But the

pathogenesis of BPH is not understood. In the last few decades, increasing evidence has emerged to demonstrate that BPH is related to chronic inflammation (66-68, 73).

In our study, like other studies, there were weak and strong points. One of the weak points of our study is the lack of laboratory measurements to investigate the molecular processes created in the bodies of patients as a result of curcumin consumption. Also, the follow-up period of the patients in our study was not long. On the other hand, our study had some strengths. First of all, this paper was one of the first randomized clinical trials to assess the impact of curcumin on controlling urinary symptoms in patients with benign prostatic enlargement who underwent endoscopic surgery. Also, as the first study, our study was able to examine an acceptable sample size of patients.

Conclusions

Our study was one of the first to assess the effects of CUR in reducing the symptoms of patients with LUTS/BPH postoperative TURP as a randomized clinical trial. The results indicated that CUR had a positive impact on reducing the symptoms of participants, but changes in nocturia were not significant.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Ethics statement

The Ethics Committee of Mashhad University of Medical Sciences approved this stufy (IR.MUMS.MEDICAL.REC.1399.630).

Data availability

Data will be provided on request.

Abbreviations

BPH	Benign prostatic hyperplasia
CUR	Curcumin
LUTS	Lower urinary tract symptoms
PD	Parkinson's disease
PSA	Prostate-specific antigen
SD	Standard deviation
TURP	Transurethral resection of the prostate

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