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Research Article

Clinical evaluation of polyherbal formulation (Uricare Tablet) in benign prostatic hyperplasia: randomized, placebo controlled, single blinded clinical study

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ABSTRACT

Background: This was a randomized, placebo controlled, single blinded clinical trial undertaken in 60 male patients in the age group of 18-70 years diagnosed with benign prostatic hyperplasia (BPH) in the department of at P.D. Patel Kayachikitsha, Ayurveda Hospital, India.
Methods: A medical history, especially on urinary symptoms was obtained from all patients on first visit along with Blood tests. 60 Patients were randomized into two groups. Uricare tablet was administered at the dose of 2 tablets twice a day for the period of 6 weeks to treatment group and Placebo tablet was administered with same doses to the remaining patients group. They were evaluated on BPH assessment parameters, IPSS (International prostate symptom score), quality of life (QOL), level of serum PSA and the prostate volume.
Results: Percentage reduction in IPSS score was observed 25.62% and 1.80% in treatment and placebo group respectively. Percentage improvement in QOL was also observed 31.67% and 2.82% in treatment and placebo groups respectively. BPH assessment parameters also show moderate changes in before and after treatment in both groups. However, the reduction in prostate volume was identified up to -4.612cc and -1.427cc in treatment and placebo group respectively at the end of the trial. Prostate significant antigen (PSA) was significantly reduced in the treatment group than Placebo group.
Conclusions: There were no serious adverse effects observed during the study. Hence, the therapy was assumed to be well tolerated by patients and can be considered as a drug of choice in the management of BPH.

Keywords: BPH, IPSS, QOL, PSA, Prostate volume

INTRODUCTION

The prostate is a single, doughnut-shaped gland about the size of a golf ball. It measures about 4 cm (1.6 in.) from side to side, about 3 cm (1.2 in.) from top to bottom and about 2 cm (0.8 in.) from front to back. It is inferior to the urinary bladder and surrounds the prostatic urethra. The prostate slowly increases in size from birth to puberty. It then expands rapidly until about age 30, after which time its size typically remains stable until about age 45, when further enlargement may occur.[1] Benign prostatic hyperplasia (BPH) is a disorder, which leads to urinary symptoms in elderly males. More than 90% of the males over 80 years of age have histological evidence of BPH.[2,3] The development of disease is also associated with enhanced proliferation and suppressed apoptosis of

prostatic cell. Polypeptide growth factors play an important role in disease development.[4]

The complications of BPH include frequency of micturition, nocturia, dysuria and urgency or urge incontinence. Acute retention of urine is an unfortunate obstructive complication. Surgery is the ultimate solution, but pharmacotherapy is often tried first and continued for as long as feasible.[5] The goal of BPH treatment is to reduce excessive cell growth by inhibiting the conversion of testosterone into the dihydrotestosterone and by preventing the attachment of estrogen to its receptors in the prostate tissue.[6] The allopathic medicines used in the treatment of BPH are associated with a number of side effects like headache, dizziness, hypotension, fatigue, reduced libido, impotence, breast tenderness, breast enlargement, and reduced sperm count which are major limitations in the long term usage of the allopathic drugs. Moreover, post-surgical complications are also more with the surgical procedures like Prostatectomy. So, phytotherapy has gained momentum as an alternative for the management of BPH worldwide.[4,5]

Hence, the prime objective of this study is evaluate the efficacy and safety of Uricare Tablet in BPH by determining the prostate volume, Level of Serum PSA and also by evaluating the IPSS score which can influence the quality of life. It is a polyherbal formulation indicated for BPH and each tablet of Uricare contains powders of Ext. *Crataeva religiosa* (Varuna) Stem and Bark, Ext. *Boerhavia diffusa* (Punarnava) Root, Ext.*Tinospora cordifolia* (Guduchi) Stem, *Commiphora mukul* (Guggulu) and Shuddha Shilajit.

Tinospora cordifolia: *Tinospora cordifolia* showed a dose dependant stimulation of the proliferation of the LNCaP cells, which helps in the treatment of the prostate cancer.[7]

Crataeva religiosa: The Ayurvedic preparation of *Crataeva religiosa* effective in the treatment of the benign prostatic hyperplasia.[8]

Boerhavia diffusa: The data suggest that *B. diffusa* significantly decreased total protein content, suggesting enzymatic changes in the prostate gland. *B. diffusa* extract contains bioactive components, which are able to relax prostatic smooth muscle and also attenuated α-receptor response at some extent. *B. diffusa* extract inhibit isolated vas deference contractility induced by noradrenaline suggest that it might have acted on α-receptor.[4]

Commiphora mukul: It supports kidney and bladder health, detoxification of the urinary tract and also support against enlarged prostate, urinary tract disorders, urinary Stones, inconsistent urination.[9]

All the raw materials are obtained from the various sources and quality controlled test are performed in the quality control department of the "Petlad mahal arogya mandal pharmacy" with the reference of the Ayurvedic Pharmacopoeia.

Name of manufacturer and commercial product: Uricare Tablet (400mg); Petlad mahal arogya mandal pharmacy, Piplata- 387355, Gujarat, India.

METHODS

This was a randomized, placebo controlled clinical trial undertaken in 60 male patients in the age group of 18-70 years diagnosed with Benign Prostatic Hyperplasia in the P.D. Patel Ayurvedic Hospital, Nadiad. The entire project was followed in the compliance of the ICH-GCP Guidelines. Informed consent form was filled by the patients before the beginning of trial. The patients were first randomized to 2 different groups by generating the single block randomization schedule in randomization.com website by the sponsor authorized clinical research associate and then divided in Treatment group and placebo group by the clinical research coordinator at investigator site, and evaluated for the hematological and biochemical parameters on the emphasis of the urinary symptoms. The entire project is registered with the CTRI Registration No: CTRI/2016/04/006824 and also approved by the "J.S. Ayurved Mahavidyalaya and P.D.Patel Ayurved Hospital, Institutional Ethics committee for Human Research" dated on 29/07/2015.

Uricare tablet was randomly administered to 30 patients at a dose of 2 tablets, twice daily for a period of 6 weeks, whereas the placebo was given to remaining 30 patients at a same dose for 6 weeks. Patient enrolled in placebo group were treated with proper treatment after end of the trial. All the patients were followed-up for 1month. Clinical evaluation will be carried out at the end of the 3months.

Inclusion criteria

a. Patients willing to fill the Informed consent form.
b. Male patients with the age between 18-70 years are included for the study.
c. Patients suffering from the BPH are included for the study.
d. Patients suffering from difficulty starting urine stream (hesitancy and straining)
e. Decreased strength of the urine stream (weak flow).
f. Dribbling after urination.
g. Feeling that the bladder is not completely empty.
h. An urge to urinate again soon after urinating.
i. Pain during urination (dysuria).

Exclusion criteria

a. Patients are not willing to submit informed consent form

b. Patients with hypertension.
c. Patients suffering from any long term autoimmune disorder
d. Patients with GI disorders and any other life threatening disorder.

Objective of study

To evaluate the benefits of Uricare tablet in terms of the following parameters.

a. Decrease of IPSS score
b. Reduction in the prostate volume
c. Decrease in bladder outlet obstruction
d. Improvement in urinary flow rate
e. Reduction in the incidence of urinary retention
f. Improvement in the quality of life

The scoring of the symptoms was done on the basis of international prostatic symptom score (IPSS) and QOL score. BPH assessment criteria is also measured at 0, 3rd and 6th week of the treatment.

Hematological and biochemical parameters were as follows:

- Blood urea and Serum Creatinine,
- Serum uric acid,
- Blood urea nitrogen,
- Prostate specific antigen (PSA)

Urine analysis report

- Color, appearance,
- pH, glucose, leukocytes, and ketone bodies

Following parameters were evaluated before and after treatment

- International prostatic symptom score (IPSS)-mild 0-7; moderate 7-19; severe 20-35
- Prostate volume by using transrectal ultra sound.
- QOL Score
- Difficulty in starting urine Stream
- Decreased strength of urine flow
- Dribbling in urination
- Pain during urination

Statistical analysis

Statistical analysis was done according to intention to treat principles. The changes in various parameters from baseline value and after 6 weeks were evaluated by "Two Tailed Paired t-test". The minimum level of significance was fixed at 95% confidence interval and 2-sided p value of <0.001 was considered significant.

The percentage calculations were performed for the Symptoms assessment criteria of BPH.

RESULTS

The 60 patients entered into the study were examined and screened before the initiation of the trial. After the screening of the patients, they were divided in two different groups (treatment group and placebo group). Informed consent form was collected from the patients or from patient's representative.

Table 1: Age group distribution.

Age group	No. of patients	% ratio
21-30	0	0
31-40	0	0
41-50	4	6.66%
51-60	40	66.66%
61-70	16	26.66%

Interestingly, patients having a tea and tobacco in any way are also directly proportionate to cause of prostate enlargement. 98.33% of the patients having 2-3 cups of the tea a day and almost 45% of the patients in contact with tobacco consumption are also tend to prostate enlargement. Those results are presented in Table 2. Most of the patients were in trouble with passing of the urine and pain in urine flow. The physiological sufferings are given in Table 3.

Table 2: Daily habits of patients.

Habit	No. of patients	% ratio
Tea	59	98.33
Tobacco	16	26.66
Smoking	11	18.33

Table 3: Urinary infection parameters.

	No. of patients suffering	
Urinary infection parameters	Present	Absent
Strong smell of urine	0	60
Trouble in passing urine	60	0
Difficulty in urine flow	60	0
Involuntary urination	1	59

The urine analysis report shows that none of the patients had any kind of the urinary infection but they all were suffering from passing of the urine up to some extent. It assumes that the patients had problems with the prostate and kidney up to some extent.

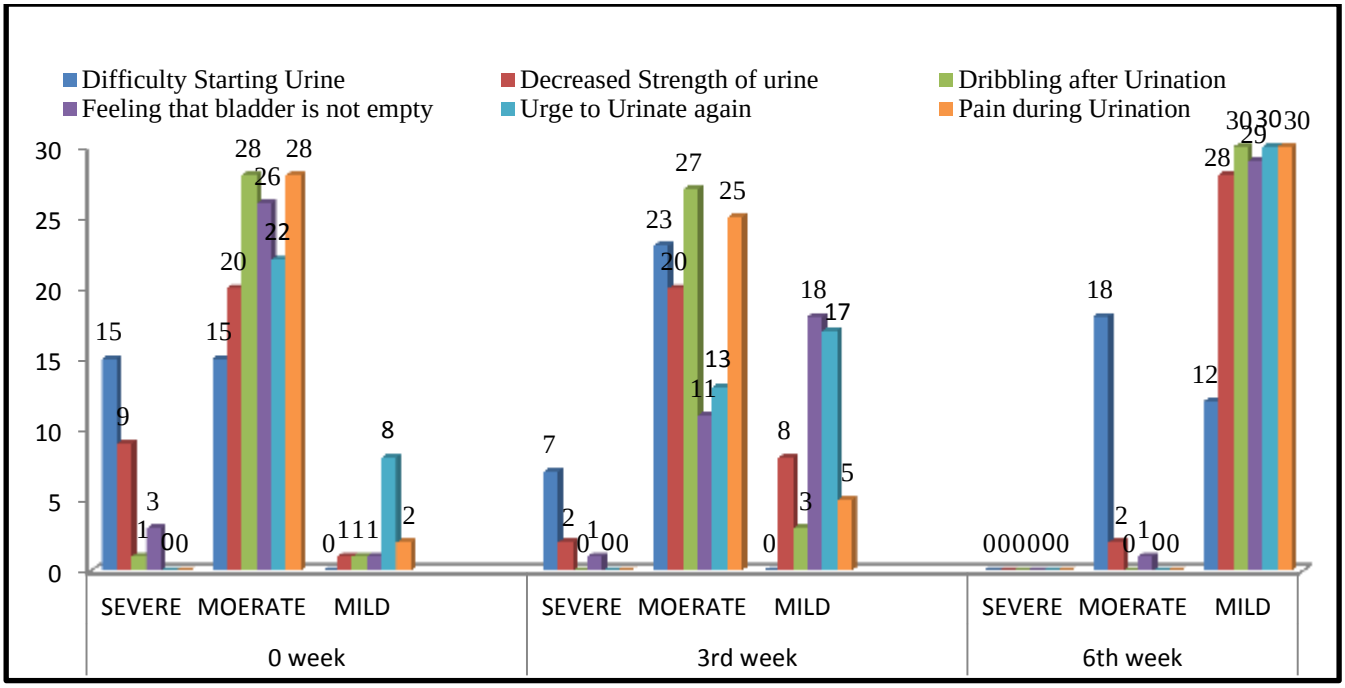

Figure 1: Prostate enlargement assessment parameters (treatment group).

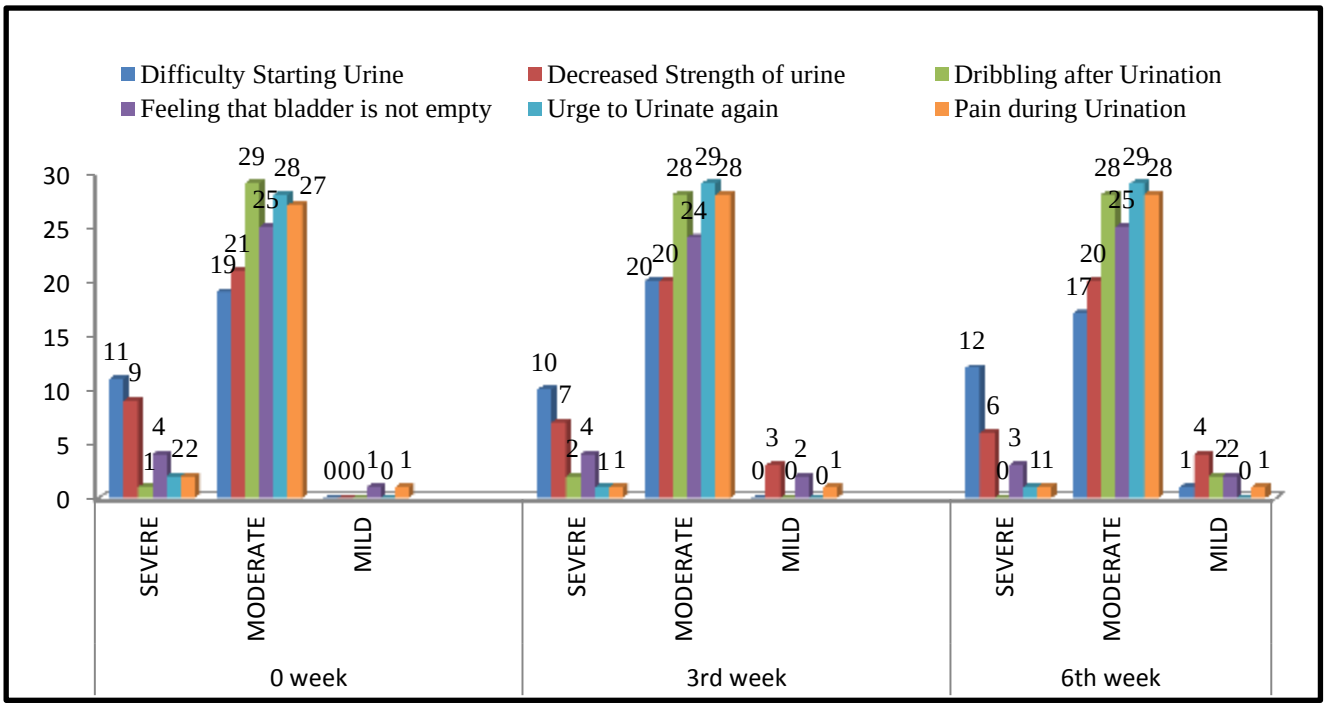

Figure 2: Prostate enlargement assessment parameters (placebo group).

Table 4: Total I-PSS score of patients.

Score	Group	Mean±SEM						
		Before	After	Paired t-test value	P value	Pearson correlation coefficient	Significantly effective	df
I-PSS	Treatment Group	17.9±0.414	8.933±0.34	26.86	p<0.0001	0.639	yes	1
	Placebo Group	19.00±0.586	18.033±0.559	26.54	p<0.0001	0.830	yes	1

Table 5: Total QOL score of patients.

Score	Group	Mean±SEM						
		Before	After	Paired t-test Value	p Value	Pearson correlation Coefficient	Significantly Effective	df
QOL	Treatment Group	3.966±0.122	2.067±0.116	17.13	p<0.0001	0.569	yes	1
	Placebo Group	4.067±0.134	3.966±0.139	1.14	p<0.0001	0.796	yes	1

Table 6: Decrease in prostate volume in Uricare tablet and placebo groups at 0 week and at the end of study.

Parameter	Treatment group		Placebo group	
	0 Week	6 week	0 Week	6 Week
Mean	30.253	25.641	30.28	28.95
Std. deviation	1.169	1.342	1.295	0.913
SEM	0.2134	0.245	0.2364	0.1666
Lower 95%CI of mean	29.82	25.14	29.9	28.61
Upper 95%CI of mean	30.69	26.14	30.86	29.29
Mean of differences	-4.612		-1.427	
95% confidence interval	-5.263 to -3.961		-1.752 to -1.102	
R squared	0.7762		0.7355	
t value	8.98		8.98	
p value	p<0.0001		p=0.4615	
P value summary	Highly significant		NS	

Table 7: Hematological parameters before and after treatment in treatment group.

Treatment Group	Blood Urea		BUN		Serum Uric Acid		Serum Creatinine		24hr albumin in urine		PSA	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Mean	27.866	26.133	12.96	12.513	4.476	4.716	0.86	0.85	78.733	82.4	6.066	3.633
Std. Deviation	5.481	4.538	2.558	2.357	0.554	0.507	0.103	0.135	12.0113	11.149	1.048	0.808
SEM	1	0.8282	0.4668	0.4302	0.1011	0.0925	0.0189	0.0247	2.1917	2.0344	0.191	0.133
Lower 95%CI of Mean	25.82	24.44	12	11.63	4.27	4.527	0.8213	0.7993	74.25	78.24	5.675	3.331
Upper 95%CI of Mean	29.91	27.83	13.92	13.39	4.684	4.906	0.8987	0.9007	83.22	86.56	6.458	3.935
Mean of Differences	-1.733		-0.447		0.24		-0.01		3.667		-2.433	
95% confidence interval	-4.447 to 0.9806		-1.718 to 0.8252		-0.05914 to 0.5391		-0.07151 to 0.05151		-1.945 to 9.279		2.722 –to 2.144	
R^2	0.05557		0.008441		0.08496		0.003797		0.05800		0.9109	
t Value	1.306		0.7027		1.641		0.3325		1.336		17.22	
p Value	0.2017		0.6636		0.235		0.3499		0.2		<0.0001	
P value Summary	NS		NS		NS		NS		NS		Highly Significant	

Table 8: Hematological parameters before and after treatment in placebo group.

Placebo Group	Blood Urea		BUN		Serum Uric Acid		Serum Creatinine		24hr Albumin in Urine		PSA	
	Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Mean	30.166	26.433	14.055	12.46	4.286	4.686	0.876	0.906	77	82.846	6.166	5.500
Std. Deviation	5.233	4.415	2.447	2.196	0.418	0.646	0.897	0.138	13.122	11.878	0.874	0.973
SEM	0.954	0.805	0.446	0.4	0.076	0.117	0.016	0.025	2.394	2.167	0.159	0.178
Lower 95%CI of Mean	28.21	24.78	13.14	11.64	4.13	4.445	0.8415	0.8541	72.1	78.41	5.840	5.136
Upper 95%CI of Mean	32.12	28.08	14.97	13.28	4.443	4.928	0.9106	0.9597	81.9	87.28	6.493	5.864
Mean of Difference	-3.733		-1.595		0.4		0.03103		5.847		-0.6667	
95% confidence interval	-6.324 to -1.143		-2.872 to -0.3176		0.1166 to 0.6834		-0.03874 to 0.1008		-0.7306 to 12.42		-0.9322 to -0.4011	
R squared	0.2305		0.1836		0.2233		0.02879		0.1023		0.4762	
t Value	2.947		2.554		2.887		0.9111		1.818		5.135	
p Value	0.4435		0.3326		0.435		0.1046		0.4796		< 0.001	
P value Summary	NS		NS		NS		NS		NS		Significant	

In the prostate enlargement assessment parameters, all patients were divided into 2 groups with 30 patients each in the group. Group 1 was considered as a treatment group and group 2 was considered as placebo group. Among the 30 patients in group1, 88.33% of the patients were treated successfully by observing the assessment criteria to mild condition. Whereas only 5.55% of patients were treated to mild condition in group 2 same time, 81.66% remain in moderate condition and 12.77% patients still remained in the severe condition of the BPH symptoms in the placebo group. The result of the prostate volume was examined by using the transrectal ultrasonography technique and it revealed the moderate reduction up to -4.612cc in the treatment group of the prostate volume at the end of the trial. There was also a moderate reduction in the placebo group might be due to the effect of the psychological effect to the patient.

DISCUSSION

The benign prostatic hyperplasia refers to an anatomic diagnosis, in practice it is typically diagnosed clinically on the basis of lower urinary tract symptoms and prostatic enlargement detected on manual rectal examination or transrectal ultrasonograph.[10] The Uricare tablet shows moderate activity in the treatment of the Prostate enlargement by showing the reduction in the I-PSS score and improving the quality of Life. Experimental study has assumed that the ingredients of Uricare tablet possesses both α-adreno receptor antagonist and 5α-reductase enzyme inhibitory activities. It might reduce the symptoms of Benign Prostatic Hyperplasia. Uricare tablet also enhances the urine flow by increasing the strength of urine, reducing dribbling after urination. It also helps in the condition of urge to urinate again after urination and by reducing the pain during urination, which indicate that the drug is more effective and safe in relieving symptoms associated with Benign Prostatic hyperplasia.[2]

Moreover, in this clinical study, particular habits of every subject was also examined which supposed to have an effective role in BPH. Surprisingly, the patients possess the habit of having tea and prone to tobacco consumption was found to have the prostate related disorders. It had been proved that all these beverages and tobacco contains caffeine and which can double the chances of the prostate enlargement and also increases the chances of prostate cancer. Another way caffeine can affect the prostate health is through its ability to irritate the bladder because theoxanthine, which is also responsible for the stimulating and irritation of the bladder.[11] Hence, drinking such caffeine contains beverages can worsen the pain associated with prostate problems and chronic prostatitis.[12]

BPH assessment symptoms were also evaluated in the both groups. It shows the significant reduction in all the

symptoms of BPH in treatment group. Whereas it shows only negligible differences in the evaluation of BPH symptoms in the placebo group.

Significant reduction of an IPSS score noticed in this study. The percentage reduction of an IPSS score in before and after trial was found to be at 25.62% in the treatment group, whereas this ratio found 1.80% in the placebo group. Hence it shows that, Percentage difference of IPSS reduction in treatment and placebo group was 23.82%.Similarly, the quality of life was improved up to 31.67% in treatment group which was also observed only 2.82% in the placebo group. Percentage improvement of QOL in treatment and placebo group was observed up to 28.85%.

Hematological and biochemical parameters were examined at initial and 6th week of the trial in all the patients to find out any significant differences. Regardless, there was no any relevant difference noticed in any patients. All parameters were laid in its normal range with negligible difference throughout the project, except prostate specific antigen (PSA). PSA was significantly reduced in the treatment group which was directly affected in reduction of the Prostate volume.

The transrectal ultrasonographic examination revealed a moderate reduction in the prostate volume in the drug treatment group, as compared to placebo at the end of the 6 weeks.

CONCLUSIONS

Present clinical trial shows the patients with old age are more prone to the prostate enlargement. Additionally, this clinical trials also proved that patients having more Tea and tobacco on daily basis also had prostate enlargement in all the cases. However, Uricare tablet is significantly effective in controlling the symptoms of benign prostatic hyperplasia by resolving the difficulty of starting of the urine, dribbling after urination and pain during the urination compare to placebo group. It also helps to reduce the feeling of heavy bladder at the end of 6-week treatment. Doctor oriented questionnaire IPSS also shows significant reduction of BPH symptoms and enhances the quality of life up to a certain level in the treatment group. Moreover, it also produces a moderate reduction of prostate volume and the Prostate Specific Antigen in the patient treated with the Uricare tablet. Additionally, the therapy does not produce any side effects in any patients during treatment; hence the therapy was well tolerated and accepted by the patients and can be considered as a drug of choice in the management of patients with benign prostatic hyperplasia at initial level.

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