

Comparative Study of the Stone Expulsion Rate after Treatment with Tamsulosin, Tadalafil and Combination of Tamsulosin and Tadalafil

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Received: 18-05-2023 / Revised: 24-06-2023 / Accepted: 26-07-2023

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Conflict of interest: Nil

Abstract:

Objective: To compare the stone expulsion rate after treatment with tamsulosin, tadalafil and combination of tamsulosin and tadalafil. , the spontaneous passage of stones, the stone expulsion time, episodes of pain and analgesic dose required and side effects of drugs were noted and compared

Methods: Study is a hospital-based observational study conducted over a period of 18 months Patients aged ≥ 18 years presenting with solitary, symptomatic ureteral stone, size of 5-10 mm were grouped into three equal drug groups. Patients was advised drugs in Group A Tamsulosin 0.4 mg, Group B Tadalafil 10 mg and Group C Tamsulosin 0.4 mg with Tadalafil 10 mg . Follow-up routine visits on day 14, 28 and as and when required in acute pain. At each follow-up visit, the spontaneous passage of stones, the stone expulsion time, episodes of pain and analgesic dose required and side effects of drugs were noted.

Results: The results of this study indicate that the use of tadalafil in comparison to tamsulosin increases the ureteric stone expulsion rate, although not statistically significant. The combination therapy of, tamsulosin and tadalafil proved to be safe and effective as demonstrated by the low incidence of side effects although more than single drug therapy but tolerable, and the increased stone expulsion rate and reduced expulsion time in comparison to single drug therapy.

Conclusion: The results of this study have shown a potentially significant role of tamsulosin, tadalafil and combination therapy for medical expulsive therapy of distal ureteral stones, broadening pharmacological spectrum of medical expulsive therapy which can be easily be provided in an outpatient setting.

Keywords: Tadalafil, Tamsulosin, Combination Therapy, Medical Expulsive Therapy.

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Introduction

In country like India where health expenditure is to be borne by patients themselves. The cost of treatment is of utmost important concern. Hence for smaller stone less costly option of medical expulsion therapy is a wiser treatment strategy. Even though the stones pass in most cases, they can cause acute pain to the patient while passing down the ureter. So, there is a further need for such agents that promote better stone passage with reduced need for surgical interventions.

The AUA and the European Urological Association ureteric stones clinical guidelines advocates the use of MET for patients with distal ureteral calculi of < 10 mm. In comparison with surgical intervention for ureteric stones, MET has a high safety profile and low cost. Medical expulsive therapy (MET) has been described as an efficacious conservative treatment option for the initial management of small distal ureteral stones. In MET, passage of the stone

is accentuated by ureteric smooth muscle relaxation, subsidence in the ureteric mucosal oedema, and an elevation in the hydrostatic pressure proximal to the stone. Various studies of efficient stone expulsion have been done for increasing the stone expulsion rate. Therapies which have been investigated includes various alpha-blockers, calcium channel blockers, corticosteroids, and most recently phosphodiesterase-5 inhibitors (PDE5) inhibitors these drugs have been tried alone and combination.

As per most of the guideline advisory α -blockers are currently the only recommended standard monotherapy. The stimulation of α -adrenergic receptors in the ureter increases the force of contraction and the frequency of peristalsis. Blockade of $\alpha 1$ -adrenergic receptor diminishes basal smooth muscle tone, frequency and amplitude of peristaltic wave, without hampering tonic propulsive contractions, that results into reduction in the intra-

ureteric pressure and fluid transportation rate enhancement hence increases the chances of stone expulsion.

Tamsulosin, which is a combination of $\alpha 1D$ and of $\alpha 1 A$ adrenergic receptors blocker increases stone expulsion rates, alleviate pain, and reduces stone expulsion time. Multiple meta-analyses have demonstrated clinically significant increases in spontaneous ureteral stone passage with the use of α - adrenergic blocker. Of the 36 randomized trials of α -adrenergic blocker for MET of stones, 30 utilized a tamsulosin arm. Spontaneous stone passage rates for α -adrenergic blocker as initial therapy in individual trials ranged from a low of 35% to a high of 100%, with the overall stone passage rate being 79%.

Gratzke et al demonstrated the role of phosphodiesterase inhibitors in relaxation of ureteric muscles. Phosphodiesterases (PDEs) controls intracellular cyclic nucleotide level affecting smooth muscle tension. PDE-5 inhibitors, act via the nitric oxide/cyclic guanosine monophosphate (cGMP)-signalling pathway, resulting in increased levels of c GMP, which leads to ureteric smooth muscle relaxation. This fact has paved way for use of tadalafil as a potential useful adjunct into the field aiming increase stone passage, shorten time to passage, and pain reduction.

Tadalafil has the advantage of longest duration of action (~36 hours) among the current PDE5 inhibitors and is associated with less visual problems. Its absorption does not appear to be affected by meals. Klöner et al demonstrated that the combination of Tamsulosin with Tadalafil did not show significant hemodynamic alteration.

The combination of tamsulosin and tadalafil is supposed to have added capability than either drug individually, for the treatment of distal ureteric stone. This combination is currently being used after approval by FDA, for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. Only limited studies has been done in recent past using these two drugs in combination for the treatment of lower ureteric stones. The purpose of the present study is a search of the best MET practice by comparing the efficacy of MET in form of tamsulosin, tadalafil alone and combination of both, Since alpha-blockers, especially tamsulosin, are proven in multiple randomized controlled trials, meta-analysis as well as recommended by EAU and AUA guidelines 21, 23 for use as MET for lower ureteric calculus of size up to 10 mm.

Role of PDE5i in this scenario is not so clear. Hence, we want to compare the efficacy of tadalafil, a PDE5i and combination therapy with the well-known drug tamsulosin in respect of stone expulsion

rate, safety, time to stone expulsion, complications during use and need of surgical intervention.

Materials and Methods

Study Design: The present study is an observational study.

Method of data collection: This study was conducted in our hospital after receiving clearance from the institutional ethics committee. The present study is a hospital-based observational study conducted over a period of 18 months from February 2017 to July 2018 at department of urology and renal transplant, Sri Aurobindo medical college and postgraduate institute, Indore.

Inclusion criteria:

Patients aged ≥ 18 years presenting with solitary, symptomatic ureteral stone, size of 5-10 mm in its greatest dimension in either of distal ureter who voluntarily decided to take part in this study and gave written consent.

Exclusion criteria:

1. Fever more than 100. F with signs of sepsis, severe hydronephrosis.
2. Patients with a solitary kidney.
3. Acute or chronic renal insufficiency.
4. Multiple ureteral stones.
5. H/O open surgery or endoscopic interventions.
6. Diabetes mellitus, peptic ulcer.
7. Concomitant treatment with steroids, calcium antagonists, or nitrates, β -blockers.
8. Patients whose urinary tracts are anatomically deformed or stenosed.

Source of Study: Patients aged ≥ 18 years found to have single lower ureteral stone (below crossing of iliac vessel as per USG KUB region or on X-RAY KUB region) 5 to ≤ 10 mm in size presented in OPD and emergency. Patients who presented with acute colic were given iv diclofenac stat followed by oral Diclofenac 50 mg sos. Patients who get relieved in a day were registered for the study after getting consent.

Sample size: Total 105 patients were finally registered and allocated in groups as per randomization based on a lottery chit method. Patients were grouped into 3 equal groups of each drug group The sample size per group was kept 35. Patients was advised drugs in Group A Tamsulosin 0.4 mg once daily and Group B Tadalafil 10 mg once daily and Group C Tamsulosin 0.4 mg with Tadalafil 10 mg both once daily.

Procedure Adopted: All patients subjected to detailed history and thorough clinical examination and following investigations done:

- CBC
- Urine R/M

- Serum creatinine
- X-RAY KUB / USG KUB Region
- NCCT KUB if clinically needed

Patient were be asked to filter their urine using a standard mesh net to detect stone expulsion. All patients were instructed to take one tablet of diclofenac Na 50 mg orally during ureteric colic episodes (maximum 150 mg /day). Follow-up routine visits on day 14, 28 and as and when required in acute pain. At each follow-up visit, the spontaneous passage of stones, the stone expulsion time, episodes of pain and analgesic dose required and side effects of drugs were noted. Date of the last positive image study and the most recent follow-up were recorded. The study medications were discontinued after spontaneous stone expulsion and complete clearance confirmed by follow up X-RAY OR USG KUB region on suspicion of stone passage, surgical intervention, or at the end of the study period (4 weeks). No expulsion of the stone at the end of the study and intervention before the end of the study as the result of uncontrolled pain or other serious events were considered as a failed therapy. Ureterorenoscopic stone removal was done if spontaneous passage of stone does not occur. The primary end point studied was the stone expulsion rate. Secondary end points studied were stone expulsion time, number of pain episodes, analgesic use, surgical intervention, and side effects related to medical therapy.

Data collection and methods: A pretested semi structured proforma was used to record the patient data. Clinical presentation, investigation (haematological and radiological), events during follow up were recorded in all patients and the data was entered in MS Excel sheet.

Ethical justification

1. All patients were provided full information in their language regarding every details of the study concerning to them.
2. Informed consent was taken from all patients.
3. No invasive work was involved in this study.
4. There were no conflicts of interest in our study as there were no sponsors for our study.
5. This study is likely to provide benefit in the medical management of patients with ureteric stone.
6. The institutional ethical committee approved our study protocol.

Statistical Analysis: All the classified and categorical data were analyzed

1. Continuous variables were described as means (95% confidence interval) and the difference

was observed by using T test. ANOVA was carried out for >2 groups.

2. Differences for categorical variables were assessed by the chi-square test
3. P value < 0.05 was considered significant.

P value < 0.01 was considered highly significant. The data was entered into a Microsoft Excel worksheet and was analyzed using the SPSS Version 20 (SPSS Inc, Chicago, IL).

Results

In our series pain is most common symptom associated with radiation in 78(74.28%) patients, nausea was next most common presentation found in 63(60%) patients followed by vomiting episodes in 26(24.76%) patients hematuria was present in 19(18.09%) patients, while dysuria in 19(18.09%) patients. Most of the patients presented to us are having Hb level in range of 12-15 mg/dl, 60 patients, creatinine level between 0.5-1 mg/dl in 73 patients. Total Leucocyte count range 5000-10000 cells/mm³ was found in 71 patients In our series tamsulosin was associated with side effects like abnormal or retrograde ejaculation in 4(11.42%) patients, postural hypotension in 5(14.28%) cases, gastritis in 3(8.5%) patients, dizziness in 2(5.7%) patients, backpain in one patient (2.8%) while tadalafil is associated with headache 6(17.14%), abnormal erection episodes 4(11.4%), gastritis and dizziness with episode of hypotension in one patient each (2.8%), combination therapy is associated with abnormal erection in 6(17.14%) patients, headache and dizziness in five patients (14.28 %) hypotension in 4(11.42%) patients back pain in 3(8.5%) patients, runny nose in 2(5.7%) patients. On applying One-way ANOVA between the three therapies given to the patients, it was found that stone expulsion time (weeks) was significantly associated. There was a statistically significant difference between groups, for stone expulsion time (weeks), as determined by one-way ANOVA ($F(2,77) = 4.782, p = 0.011$). There was no statistically significant difference between Tadalafil and combination of both drugs ($p=0.877$). Similarly, there was no statistically significant difference between and Tadalafil (1.89+0.875 weeks, $p=0.057$) and Tamsulosin (2.50+1.102 weeks). On applying chi-square test, $\chi(1) = 4.786, p = 0.027$ which means there was statistically significant association between Tamsulosin and Combination of Tamsulosin and Tadalafil groups and stone expulsion rate. That indicates, given combination of Tamsulosin and Tadalafil, stone expulsion rate is significantly higher than only Tamsulosin group.

Table 1: Distribution of Symptoms in Patients with the 3 Regimens

Therapy given	Pain		Radiation		Hematuria		Dysuria		Nausea		Vomiting	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present
Tamsulosin	0	35	10	25	25	10	23	12	10	25	24	9
Tadalafil	0	35	10	25	30	5	32	3	15	20	29	6
Combination of both	0	35	7	28	31	4	31	4	17	18	24	11
Grand Total	0	105	27	78	86	19	86	19	42	63	77	26

Table 2: Spectrum of Blood Investigations

Sr.No	Investigations			
1	Hb level	8-11 mg/dl	12-15 mg/dl	>15 mg/dl
	Number of patients	39	60	6
2	Creatinine	0-0.5 mg/dl	0.5-1 mg/dl	>1 mg/dl
	Number of patients	9	73	25
3	Total Leucocytecount	<5000 cells/mm ³	5000-10000 cells/mm ³	>10000 cells/mm ³
	Number of patients	2	71	32

Table 3: Distribution of Drug Therapy Side Effects

Therapygiven	Headache		Dizziness		Postural hypotension		Backpain		Runny nose		Gastritis	
	A	P	A	P	A	P	A	P	A	P	A	P
Tamsulosin	35	0	32	2	30	5	34	1	35	0	32	3
Tadalafil	29	6	34	1	34	1	34	1	35	0	32	3
Combination of both	30	5	30	5	31	4	32	3	33	2	35	0
GrandTotal	94	11	97	8	95	10	100	5	103	2	99	6
Therapygiven	Abnormal erection				Abnormal ejaculation							
	Absent		Present		Absent		Present					
Tamsulosin	35		0		31		4					
Tadalafil	31		4		35		0					
Combination of both	29		6		35		0					
Grand Total	95		10		101		4					

Table 4: Association between Three Therapies Given and Age, Stone Size and Analgesic Dose One way ANOVA Descriptive

Parameters	Therapy Given	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval For Mean	
						Lower Bound	Upper Bound
Age	Tamsulosin	35	31.06	9.337	1.578	27.85	34.26
	Tadalafil	35	33.83	10.837	1.832	30.11	37.55
	Combination of Both	35	33.29	12.704	2.147	28.92	37.65
	Total	105	32.72	11.005	1.074	30.59	34.85
Stone Size	Tamsulosin	35	7.02	1.454	0.246	6.52	7.52
	Tadalafil	35	6.80	1.232	0.208	6.38	7.22
	Combination of Both	35	7.34	1.474	0.249	6.84	7.85
	Total	105	7.05	1.396	0.136	6.78	7.32
Analgesic Dose	Tamsulosin	35	391.43	165.603	27.992	334.54	448.32
	Tadalafil	35	287.14	144.173	24.370	237.62	336.67
	Combination Of Both	35	268.57	166.312	28.112	211.44	325.70
	Total	105	315.71	166.600	16.258	283.47	347.96
One way ANOVA							
		Df	Mean Square	F	Sig.		
Age	Between Groups	2	75.495	0.619	0.541		
	Within Groups	102	122.000				
	Total	104					
	Between Groups	2	2.609	1.349	.264		
	Within Groups	102	1.935				

Stone Size	Total	104			
Analgesic Dose	Between Groups	2	153500.000	6.070	.003
	Within Groups	102	25289.916		
	Total	104			

Table 6: Association between the Three Therapies Given and Stone Expulsion Time

Descriptive statistics								
Stone Expulsion Time (weeks)								
Therapy given	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Tamsulosin	22	2.50	1.102	0.235	2.01	2.99	1	4
Tadalafil	28	1.89	0.875	0.165	1.55	2.23	1	4
Combination of Tamsulosin and Tadalafil	30	1.73	0.785	0.143	1.44	2.03	1	4
Total	80	2.00	0.955	0.107	1.79	2.21	1	4
One-way ANOVA								
Stone Expulsion Time (weeks)								
	Sum of Squares	df	Mean Square	F	Sig.			
Between Groups	7.955	2	3.977	4.782	.011			
Within Groups	64.045	77	.832					
Total	72.000	79						

Table 7: Association between the Three Therapies Given and Pain Episodes

Descriptive Statistics								
Pain Episodes								
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Tamsulosin	35	6.26	2.582	0.436	5.37	7.14	2	10
Tadalafil	35	4.51	2.318	0.392	3.72	5.31	1	8
Combination of Tamsulosin and Tadalafil	35	4.23	2.486	0.420	3.37	5.08	1	8
Total	105	5.00	2.602	0.254	4.50	5.50	1	10
One-way ANOVA								
Pain Episodes								
	Sum of Squares	df	Mean Square	F	Sig.			
Between Groups	84.400	2	42.200	6.947	.001			
Within Groups	619.600	102	6.075					
Total	704.000	104						

On applying One-way ANOVA between the three therapies given to the patients, it was found that pain episodes were highly statistically significantly associated.

Table 8: Association between Tamsulosin and Tadalafil Groups and Stone Expulsion

Drug groups * Expulsion rate Cross tabulation					
Sr. No.	Drug groups	Number of patients and percentage	Stone expulsion		Total
			Yes	No	
1	Tamsulosin	Count	22	13	35
		% within Drug groups	62.9%	37.1%	100.0%
2	Tadalafil	Count	28	7	35
		% within Drug groups	80.0%	20.0%	100.0%
	Total	Count	50	20	70
		% within Drug groups	71.4%	28.6%	100.0%

On applying chi-square test, $\chi(1) = 2.520$, $p = 0.093$ which means there was no statistically significant association between Tamsulosin and Tadalafil groups and stone expulsion rate.

Table 9: Association between Tamsulosin and Combination of Tamsulosin and Tadalafil Groups and Stone Expulsion

Drug groups * Expulsion rate Crosstabulation					
Sr NO	Drug groups	Number of patients andpercentage	Stone expulsion		Total
			Yes	No	
1	Tamsulosin	Count	22	13	35
		% within Drug groups	62.9%	37.1%	100.0%
2	Combination of Tamsulosin and Tadalafil	Count	30	5	35
		% within Drug groups	85.7%	14.3%	100.0%
	Total	Count	52	18	70
		% within Drug groups	74.3%	25.7%	100.0%

Table 10: Surgical Interventions Done in the Patients

Drug group	Intervention done	
	No	Yes
Tamsulosin	29 (82.2%)	6 (17.1%)
Tadalafil	32 (91.4%)	2 (5.7%)
Combination of both	35 (100%)	0
Grand Total	97 (92.3%)	8 (7.6%)

Discussion

Colic episode: Colicky pain in ureteric colic is pain which occurs due to intraureteric pressure increment proximal to stone in our series that pain episode was statistically significantly lower after taking

combination of both drugs (4.23+2.486, p=0.002) and Tadalafil (4.51+2.318, p=0.011) compared to Tamsulosin (6.26+2.582). There was no statistically significant difference between Tadalafil and combination of both drugs (p=0.879).

Table 11:

Study	Tamsulosin	Tadalafil	Tamsulosin + Tadalafil
Kumar et al	1.60 ± 1.0	0.45 ± 0.68	
Goyal et al	0.62 ± 0.83	0.96 ± 0.74	
Santosh et al	1.60 ± 1.00		0.45 ± 0.68
Our study	6.26 ± 2.582	4.51 ± 2.318,	4.23 ± 2.486,

Colic Episodes Kinnman et al. described use of α -blockade may help in ureteric colic by blocking the pain mediating C-fibers. Use of α -blockers for expulsion of ureteric stones probably decreases the analgesic requirement in two ways: expulsion of stones and blockade of C-fibers. Thus, it is difficult to assess which of these may be primarily responsible for decreasing the analgesic requirement. The stimulation of alpha 1 adrenergic receptors increases ureteral peristaltic frequency, smooth muscle tones and contractile force, resulting in

ureteral spasm and decreased ureteral flow. Less episodes of pain in combination therapy may be attributed to synergistic smooth muscle relaxation and anti-inflammatory action of tadalafil by various mode of action suggested in many different studies.

Analgesic Dose: In our series analgesic dose was statistically significantly lower after taking combination of both drugs, p=0.005) and Tadalafil (287.14+144.17mg, p=0.020) compared to Tamsulosin (391.43+165.60).

Table 12:

Study	Tamsulosin	Tadalafil	Tamsulosin + Tadalafil
Kumar et al	2.90 ± 0.90	1.87 ± 0.8	
Goyal et al	9.15 ± 3.80	11.82 ± 3.34	
Santosh et al	2.90 ± 0.90		1.87 ± 1.38
S. raza et al	406 + 182	346 + 201	476 + 209
Our study	391.43 ± 165.60	287.14 ± 144.17	268.57 ± 166.31

Analgesic Dose These effects of the combined use of tamsulosin and tadalafil on the ureter were probably due to a decrease in the frequency and amplitude of the phasic peristaltic contractions that accompany ureteric obstruction, i.e., an improved antispasmodic effect.

Side Effects: In our series tamsulosin was associated with side effects like abnormal or retrograde ejaculation in 4(11.42%) patients, postural hypotension in 5 (14.28%) cases, gastritis in 3 (8.5%) patients, dizziness in 2 (5.7%) patients, backpain in one patient(2.8%) while tadalafil is

associated with headache 6 (17.14%), abnormal erection episodes 4 (11.4%), gastritis and dizziness with episode of hypotension in one patient each (2.8%), combination therapy is associated with abnormal erection in 6(17.14%) patients, headache and dizziness in five patients(14.28 %) hypotension in (11.42%) patients back pain in 3 (8.5%) patients, runny nose in 2(5.7%) patients. All the patients who felt penile erection mild degree of penile tumescence was mild lasting up to half an hour, offending agent is tadalafil alone or as a part of combination therapy but no patients developed priapism. There were no

serious side effects was found in any of the groups probably because of the lack of any associated comorbidity and wisely chosen exclusion criteria. Similar to our study in study of Kumar et al drug-related adverse effects, occurred more in combination therapy such as headache, dizziness, orthostatic hypotension and backache, occurred. Abnormal ejaculation was most significant finding seen in upto 18.3% with tamsulosin & 12.3% in combination therapy patients.

Stone Expulsion Time:

Table 13:

Study	Tamsulosin	Tadalafil	Tamsulosin + Tadalafil
Kumar et al (days)	16.7 ± 4.8	14.9 ± 4.4	
Goyal et al Expulsion time(days)	9.38±6.66	9.61±7.47	
Boulos v et (days)	14.5±3.9 days	17.2±4.3	
Santosh et al	16.7 ± 4.8		14.9 ± 4.4
Our study(weeks)	2.50+1.102	1.89+0.875	1.73+0.785

Table 14: Stone Expulsion Rate:

Study Expulsion rate (%)	Tamsulosin	Tadalafil	Tamsulosin + Tadalafil
Kumar et al	65.5 %	83.6 %	
Goyal et al	73 %	69 %	
Boulos v et al	64 %	84 %	
Santosh Kumar	74.2 %		83.9%
S Raza et al	70 %	73 %	76%
Abhishek et al	74 %	80%	
Our study	62.9 %	80 %	85 %

Conclusion

The results of this study have shown a potentially significant role of tamsulosin, tadalafil and combination therapy for medical expulsive therapy of distal ureteral stones, broadening pharmacological spectrum of medical expulsion therapy which can be easily be provided in an outpatient setting. The results of this study indicate that the use of tadalafil in comparison to tamsulosin increases the ureteric stone expulsion rate, although not statistically significant. The combination therapy of, tamsulosin and tadalafil proved to be safe and effective as demonstrated by the low incidence of side effects although more than single drug therapy but tolerable, and the increased stone expulsion rate and reduced expulsion time in comparison to single drug therapy. Moreover, combination medical expulsive therapy considerably decreased the analgesic use thereby reducing additional need for pain relief and served as an efficient bridge between expectant management and surgical intervention

Limitations of the Study

The limitation of our study is the comparatively small sample size, but the study is still valuable as this study is among very few studies in which 3 arms have been tested. Furthermore, to our knowledge, this is the comparison study of tamsulosin with tamsulosin and tadalafil and produced some

insightful results that should be tested in future studies.

Another limitation of the present study is that NCCT KUB was not done to assess the ureteric stone because of financial Constraints in developing country and combination therapy of drugs increases the cost of treatment.

Declarations:

None Availability of data and material: Department of Urology and Renal Transplant, Sri Aurobindo Medical College and Postgraduate Institute, Indore. Code availability:

Not applicable Consent to participate: Consent taken Ethical Consideration: There are no ethical conflicts related to this study. Consent for publication: Consent taken

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