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AAHKS Award Paper

The AAHKS Clinical Research Award: Oral Dexamethasone Following Total Knee Arthroplasty: A Double-Blind, Randomized Controlled Trial

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ABSTRACT

Background: Intravenous dexamethasone has been shown to reduce pain in total joint arthroplasty. This double-blind, randomized, placebo-controlled trial investigated the postoperative effects and safety of oral dexamethasone as a potential augment to multimodal pain management in outpatient knee arthroplasty.
Methods: The authors prospectively randomized 109 consecutive patients undergoing primary total knee arthroplasty. Patients assigned to Group A (57 patients) received 4 mg of dexamethasone by mouth twice per day starting postoperative day (POD) 1 for 4 days and those assigned to Group B received placebo capsules. All healthcare professionals and patients were blinded to group allocation. The primary outcome was defined as postoperative pain scores. Secondary outcomes included 90-day postoperative complications, nausea and vomiting, daily opioid usage, assistance for ambulation, difficulty sleeping, and early patient reported outcomes. Demographics were similar between groups.
Results: The patients who received dexamethasone had a statistically significant decrease in VAS scores when averaging POD 1 to 4 ($P = .01$). The average VAS scores among individual days were significantly lower with dexamethasone on POD 2, 3, and 4. While taking dexamethasone, morning and mid-day VAS scores were significantly lower. There was no difference between the groups with opioid use, nausea or vomiting, 90-day complications, ability to walk with/without assistance, difficulty sleeping, and early patient reported outcomes.
Conclusion: This double-blind, randomized, placebo-controlled trial demonstrated that oral dexamethasone following primary total knee arthroplasty can reduce postoperative pain. This may be a beneficial option in ambulatory surgery where intravenous limitations exist, but larger series are needed to further evaluate the safety profile in this population.

Total knee arthroplasty (TKA) is one of the most successful surgical treatment options for managing end-stage knee arthritis [1]. Over recent years, there has been a push from healthcare systems, insurance companies, and the federal government for orthopaedic surgeons to perform ambulatory total joint arthroplasty [2–4]. Along with this change in patient disposition, surgical teams have sought to optimize preoperative, intraoperative, and postoperative protocols to accommodate same-day discharge as well as maintain patient surgical outcomes.

Multimodal pain protocols have become standard in orthopaedics for enhanced recovery after surgery to aid in early postoperative discharge as well as decrease opioid utilization in patients undergoing total joint arthroplasty [5–8]. One well-studied medication over the last decade has been the administration of intravenous dexamethasone preoperatively as well on postoperative day (POD) one. Intravenous (IV) dexamethasone has been shown to be a safe and effective medication to decrease postoperative pain as well as nausea and vomiting following an orthopaedic procedure [9–11].

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Before increasing our volume of ambulatory TKA, patients received a dose of IV dexamethasone on POD 1. However, with the recent drive toward ambulatory arthroplasty, patients were unable to receive IV dexamethasone on POD 1. The purpose of this double-blind, randomized, placebo-controlled trial aimed to investigate the postoperative effects and safety of oral dexamethasone, primarily in patient pain scores. The authors hypothesized that oral dexamethasone is not only safe after a TKA, but also an effective addition to the multimodal regimen to control pain in the immediate postoperative period.

Methods

This study was a prospective, randomized, double-blind, placebo-controlled study approved by the local institutional review board and enrolled on clinicaltrials.gov as registration number NCT04432259. Adult patients scheduled for elective, unilateral, primary TKA were recruited and consented for participation in the study. All surgeries were performed by 4 fellowship-trained adult reconstruction surgeons at 2 sites within a single health system in southeast Michigan. Patients were recruited from August 1, 2020 to September 30, 2021. The study exclusion criteria included patients with uncontrolled diabetes (HbA1C, >7.5%), impaired hepatic function (child class, >B), impaired renal function (glomerular filtration rate <60 mL/min/1.73 m^2), chronic opioid use (filled opioid medication ×2 within 6 months of the surgery), alcohol dependence, patients who had a known adverse reaction to corticosteroids, and patients unable to give informed consent.

Participants who were enrolled and consented to the study were assigned to 2 distinct arms of the study—Group A received 4 mg of dexamethasone by mouth twice per day starting postoperative day (POD) 1 for 4 days and Group B received placebo capsules. There were 109 patients enrolled in the study with 57 patients in Group A (Dexamethasone) and 52 patients enrolled in Group B (Placebo). The division of primary TKA within the study period and enrollment is represented in Figure 1. Demographics and baseline characteristics were similar between the groups (Table 1). There were no significant differences in age, sex, body mass index (BMI), history of smoking, history of diabetes mellitus, and preoperative American Society of Anesthesiologists (ASA) scores.

The study pharmaceuticals were capsulized by the institution's research pharmacy based on the randomization performed by a nonparticipation research assistant in the department of orthopaedic surgery. All patients received spinal anesthesia and a single dose of intravenous 10 mg dexamethasone preoperatively. All patients had ondansetron 4 mg every 6 hours available to them postoperatively in the recovery room or if calling for nausea pills while at home. Each group received a standard postoperative pain protocol which included scheduled nonsteroidal anti-inflammatory drugs, acetaminophen, and a muscle relaxer as well as oxycodone 5 mg every 6 hours as needed.

Patients were provided a daily pain journal upon discharge from the hospital on POD 0. The journal included 3 time points per day (morning, midday, bedtime) in which the patient provided a VAS score (1-10) as well as a check box if they experienced nausea or vomiting. The patient was also asked to provide the number of oxycodone pills they had taken within the 24-hour period, if they were able to ambulate with or without an assistive device, as well as if they were experiencing difficulty sleeping. Following

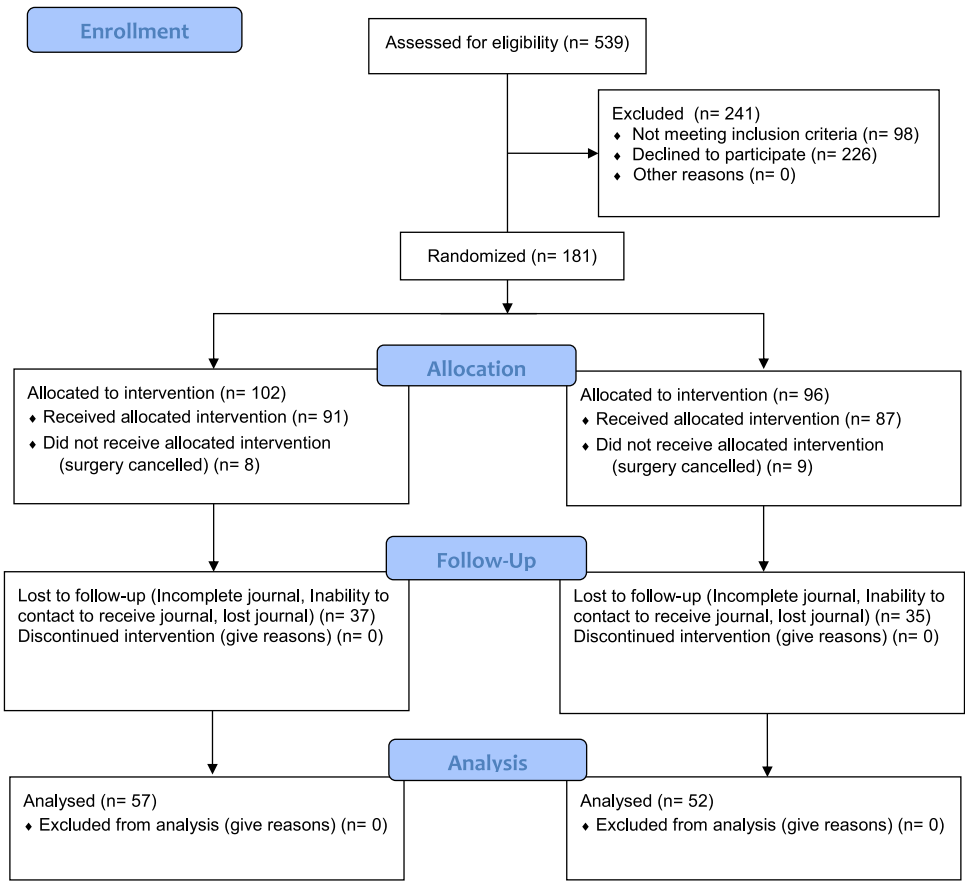

Fig. 1. CONSORT 2010 Flow Diagram.

Table 1
Patient Demographics and Baseline Characteristics.

Covariate	Statistics	Level	Medication		*P* Value[a]
			A N = 57	B N = 52	
Sex	N (Col %)	Women	33 (57.9)	35 (67.31)	.311
	N (Col %)	Men	24 (42.1)	17 (32.7)	
Side	N (Col %)	Left	31 (54.4)	18 (34.6)	**.038**
	N (Col %)	Right	26 (45.6)	34 (65.4)	
Smoking	N (Col %)	Current	6 (10.5)	5 (9.6)	.393
	N (Col %)	Never	35 (61.4)	26 (5)	
	N (Col %)	Previous	16 (28.1)	21 (40.4)	
Diabetes Mellitus	N (Col %)	No	44 (77.2)	46 (88.5)	.121
	N (Col %)	Yes - Type 2 Diabetes Mellitus	13 (22.8)	6 (11.5)	
ASA	N (Col %)	I	2 (3.5)	3 (5.8)	.583
	N (Col %)	II	29 (50.9)	30 (57.7)	
	N (Col %)	III	26 (45.6)	19 (36.5)	
Assistive Device	N (Col %)	No	31 (54.4)	33 (63.5)	.336
	N (Col %)	Yes	26 (45.6)	19 (36.5)	
Age (range)	N		57	52	.915
	Mean		64 (46-82)	64 (40-82)	
Body Mass Index	N		57	52	.431
	Mean		31.6	32.5	
	Median		31.2	30.4	

Bolded *P* values were statistically significant.
ASA, American society of Anaesthesiologists; Col, column.
[a] The parametric *P* value is calculated by analysis of variance for numerical covariates and chi-square test for categorical covariates.

completion of the written pain journal, the patients returned them to the study team via mail for input and analysis.

Basic preoperative demographics included age, sex, body mass index, history of smoking, history of diabetes mellitus, preoperative ASA score, and use of preoperative assistive device. The 90-day postoperative events comprised of emergency department visits, unplanned readmission following an outpatient procedure, periprosthetic joint infection, wound dehiscence, deep venous thrombosis, pulmonary embolism, and return to operating room. Knee injury and osteoarthritis outcome score (KOOS JR.) was utilized to interpret preoperative and 4-week to 6-week postoperative patient-reported outcomes. Besides postoperative wound dehiscence and prosthetic joint infections, which were chart reviewed by the authors up to August 1, 2022, all other variables were obtained through the Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI) as inputted by dedicated abstractors for accuracy.

All data analyses were done using SAS 9.4 (SAS Institute Inc, Cary, North Carolina) and statistical significance was set at $P < .05$. All continuous data were described using means and medians; while categorical data were described using counts and percentages. Analysis of variances (ANOVA) were used to test the difference between medications for continuous variables and Chi-squared tests were used for categorical variables. A minimal clinically important difference (MCID) was calculated utilizing half the standard deviation of the collective cohort's VAS scores on POD 1 to 4 and comparing it to the mean differences in pain scores that reached statistical significance.

Power Analyses

The cohorts were divided into a sample size of 50 per group for a total of 100 individuals. Since this was the first oral dexamethasone study in orthopaedic literature the research team used previous IV dexamethasone studies to complete a power analysis. The sample size was calculated to detect a mean difference of 1.2 points in the VAS score between the 2 groups. The means and standard deviation VAS scores at 24 hours postoperatively in patients who received IV corticosteroid were approximately 4.45 and 2.10 points, respectively [9,12]. For a 2-sided alpha of 0.05 and power of 80%, the calculated sample was 50 patients per arm (including 10% dropout).

Results

There were several statistically significant findings in regards to the postoperative VAS scores (Table 2). When averaging the recorded VAS scores during the first 4 postoperative days, a time period at which point patients were taking oral dexamethasone, those receiving oral dexamethasone experienced significantly less pain (3.77 versus 4.52; $P = .010$). When averaging VAS scores the first 7 days postoperatively, the patients did not have significantly lower scores ($P = .118$).

When dividing the average VAS score per day, patients on oral dexamethasone experienced statistically less pain on day 2 (3.71 versus 4.98, $P < .001$), day 3 (3.55 versus 4.24, $P = .040$), and day 4 (3.35 versus 4.01, $P = .048$). The average VAS score on day 1 did not demonstrate statistical significance between the 2 groups (4.45 versus 4.83, $P = .287$). Throughout the day, the average VAS scores on days 1-4 changed per timepoint recorded by the patient.

Table 2
Covariate Analyses of Postoperative Pain and Opioid Medications.

Covariate	Statistics	Medication		*P* Value[a]
		A N = 57	B N = 52	
Average VAS Score Day 1	N	57	52	.287
	Mean	4.5	4.8	
	Median	4.6	4.8	
Average VAS Score Day 2	N	57	52	**<.001**
	Mean	3.7	5.0	
	Median	3.7	5	
Average VAS Score Day 3	N	57	52	**.040**
	Mean	3.55	4.24	
	Median	3.33	4	
Average VAS Score Day 4	N	57	51	**.048**
	Mean	3.35	4.01	
	Median	3.17	3.67	
Average VAS Score Days 1-4	N	57	52	**.010**
	Mean	3.77	4.52	
	Median	3.42	4.47	
Average VAS Score Days 1-7	N	57	52	.118
	Mean	3.75	4.21	
	Median	3.43	4.25	
Average Morning VAS Score (Days 1-4)	N	57	52	**.006**
	Mean	3.81	4.63	
	Median	3.8	4.38	
Average Afternoon VAS Score (Days 1-4)	N	57	52	**.005**
	Mean	3.64	4.45	
	Median	3.63	4.5	
Average Evening VAS Score (Days 1-4)	N	57	52	.052
	Mean	3.85	4.46	
	Median	3.5	4.5	
Number of Oxycodone Day 1	N	55	49	.517
	Mean	3.27	3.63	
	Median	3	3	
Number of Oxycodone Day 2	N	56	48	.055
	Mean	3.02	4.17	
	Median	3	3	
Number of Oxycodone Day 3	N	53	47	.087
	Mean	2.3	3.26	
	Median	2	2	
Number of Oxycodone Day 4	N	55	46	.198
	Mean	2.24	2.93	
	Median	2	1	

Bolded *P* values were statistically significant.
Several of the VAS score parameters were statistically significant between the cohorts. The number of opioids was not statistically significant.
VAS, visual analog scale.
[a] The parametric *P* value is calculated by analysis of variances for numerical covariates and chi-squared test for categorical covariates.

Those on oral dexamethasone had statistically lower pain at timepoint 1 (morning) and timepoint 2 (midday) ($P = .006$, $P = .005$, respectively). Timepoint 3 (bedtime) trended toward statistical significance (3.85 versus 4.46, $P = .052$).

The standard deviation of the VAS scores throughout POD 1 to 4 was 1.99. An MCID of 1.00 was calculated utilizing half the standard deviation. Day 2 average VAS scores reached MCID when comparing the average differences ($\Delta = 1.27$). All other significant VAS scores were under the calculated MCID by 0.18-0.34.

In regards to the amount of oxycodone, neither group demonstrated a significant difference in the number of pills taken per day (Table 2). However, for each day of treatment (1-4), patients on oral dexamethasone took less oxycodone. Importantly, there were no differences in 90-day postoperative complications, which included wound complications, between the 2 groups. None of the 109 patients within the 2 groups reported nausea or vomiting postoperatively or the consumption of ondansetron. There was no difference between the groups in regards to a patient's ability to walk with or without assistance. No patient had difficulty sleeping on oral dexamethasone compared to the patients not on the corticosteroid. Neither group reported significant differences in KOOS, JR. scores (Table 3).

Table 3
Covariate Analysis of Postoperative Outcomes, Reported Walking, Reported Sleeping, and Early Patient Reported Outcomes.

Covariate	Statistics	Level	Medication		*P* Value[a]
			A N = 57	B N = 52	
Postoperative Events	N (Col %)	Emergency Department Visit	2 (3.57)	5 (10.2)	.227
	N (Col %)	No 90-Day Postop Events	54 (96.43)	42 (85.71)	
	N (Col %)	Periprosthetic Joint Infection	0 (0)	1 (2.04)	
	N (Col %)	Unplanned Admission After Outpatient Procedure	0 (0)	1 (2.04)	
Able to Walk Day 1	N (Col %)	No	2 (4.17)	4 (8.51)	.276
	N (Col %)	With Assistance	17 (35.42)	22 (46.81)	
	N (Col %)	Without Assistance	29 (60.42)	21 (44.68)	
Able to Walk Day 2	N (Col %)	With Assistance	18 (36.73)	22 (50)	.197
	N (Col %)	Without Assistance	31 (63.27)	22 (50)	
Able to Walk Day 3	N (Col %)	No	0 (0)	1 (2.33)	.332
	N (Col %)	With Assistance	13 (27.66)	16 (37.21)	
	N (Col %)	Without Assistance	34 (72.34)	26 (60.47)	
Able to Walk Day 4	N (Col %)	With Assistance	9 (18.75)	11 (26.19)	.397
	N (Col %)	Without Assistance	39 (81.25)	31 (73.81)	
Difficulty Sleeping Day 1	N		28	18	.186
	Mean		0.46	0.67	
	Median		0	1	
Difficulty Sleeping Day 2	N		32	20	.331
	Mean		0.56	0.7	
	Median		1	1	
Difficulty Sleeping Day 3	N		28	22	.422
	Mean		0.43	0.55	
	Median		0	1	
Difficulty Sleeping Day 4	N		26	22	.760
	Mean		0.5	0.55	
	Median		0.5	1	
Preoperative KOOS, JR. Score	N		53	48	.472
	Mean		45.68	47.71	
	Median		47	48.75	
Postoperative KOOS, JR. Score	N		48	47	.986
	Mean		65.06	65.1	
	Median		64	64	

There was no statistical significance in the secondary variables of the study which included postoperative outcomes.
KOOS, knee injury and osteoarthritis outcome score.
[a] The parametric *P* value is calculated by analysis of variances for numerical covariates and chi-squared test for categorical covariates.

Discussion

This prospective, double-blind, randomized, placebo-controlled trial assessed the impact of oral dexamethasone, primarily with pain control, following a TKA. Powered for reported VAS scores, the findings of this study demonstrated that while on postoperative oral dexamethasone, patients conveyed statistically significant decreases in pain scores. Interestingly, VAS scores were similar on POD 1 as one may expect with the divergence occurring the following days when oral dexamethasone would be in the patient's system while the placebo group would be further removed from the initial preoperative surgical dose. While daily VAS scores only hit MCID on POD 2, the sum total of the study period (POD 1 to 4) was also statistically significant after the standardized preoperative IV dose, which imparts efficacy of the intervention in total. Although not powered for such rare findings, there were no significant differences in 90-day postoperative complications, including wound dehiscence. There was no difference in oxycodone taken per day; however, there were trends in the dexamethasone cohort. The patients on oral corticosteroids experience no change in sleep, nor any change in postoperative nausea or vomiting. There was no significant difference in early patient reported outcomes.

This study originated from similar regimens of oral dexamethasone that have become standard of care for nausea prevention in highly ematogenic chemotherapy [13]. Particularly when patients are given Cisplatin or Doxorubicin/Cyclophosphamide, multiple organizations endorse a triple combination regimen of a neurokinin-1 receptor antagonist, serotonin type-3 RA, and dexamethasone ± olanzapine as the evidence-based approach [14,15]. This multimodal approach for nausea has translational benefit to total joint arthroplasty as it may theoretically piggyback off our known utility of IV dexamethasone to improve pain control as well.

Pain control following total joint arthroplasty has been a popular topic in orthopaedic literature especially with the dawn of ambulatory surgery [16–19]. Appropriate pain control following a total joint arthroplasty has been shown to decrease lengths of stay and improve postoperative outcomes [16,20–24]. Multimodal pain control has also been a popular research topic since the recognition of the opioid epidemic, and surgeons have taken on an initiative to reduce the number of prescribed opioids following orthopaedic surgery [5–7]. There is no consensus on the ideal multimodal pain protocol in total joint arthroplasty. Intravenous dexamethasone given postoperative day 1 has been shown in the literature to provide benefit beyond just the single day of surgery dose; however, it is not the ideal mode of medication delivery in same-day discharge surgery [9–11]. Therefore, this study demonstrated that patients on extended postoperative oral dexamethasone experienced statistically significant decreases in VAS pain scores, especially in the morning and afternoon. Whether this decrease was clinically relevant is up for debate and future trials with a larger cohort should investigate further. However, combined with the safety profile, these results mesh with prior IV dexamethasone studies showing statistical improvement in pain which makes the oral corticosteroid concept a logical outpatient option.

It should be noted that we utilized a lower dose of dexamethasone based off system comfort with standardized IV dosing perioperatively and the known precedent of such extended dosages with chemotherapy protocols utilized at our institution. However, ranges of dosing do exist for the more immediate perioperative day in the arthroplasty literature that utilize dexamethasone dosing several times larger. In a recent randomized controlled trial during TKA, Nielsen et al [25]. found benefit to a much higher single dose at 1 mg/kg versus an intermediate dose of 0.3 mg/kg. They also noted an increase in pain the next evening regardless of the dosage, calling for a potential role for additional dosing to prolong the attenuating effect a corticosteroid can yield. Our dosage was on the lower end of the historically intermediate range of 0.1-0.3 mg/kg. Studies over several decades in other surgical subspecialties noted no benefit to low dose (<0.1 mg/kg) dexamethasone as a single perioperative adjunct illustrating the dose-dependent spectrum of response [13,25,26].

The concerns with dexamethasone should not be ignored, as there exists a side effect profile for corticosteroids [27]. The most notable has been the poorly understood association with osteonecrosis, though usually from higher doses or prolonged administration. However, reports with even shorter exposures have raised conflicting concerns. Corticosteroids are also reported to cause anxiety and hyperactivity, which may disrupt a patient's sleep [28,29]. Although a secondary finding, no patients taking oral dexamethasone reported disruption of sleep postoperatively while on the medication. Another major concern with the use of corticosteroids postoperatively is the reported decrease in wound healing as an immunomodulator [26]. This study investigated 90-day postoperative complications, which included wound dehiscence, and there was no increase in return to the operating room or wound problems. Through a manual chart review in August of 2022, the study also investigated return to the operating room for prosthetic joint infection, which yielded no reported infections. This is similar to the recent work by Heckmann et al [30]. that analyzed a national database of over a million contemporary arthroplasties and found no increased risk of infectious complications with intraoperative dexamethasone. For both total hip and knee arthroplasty, they actually found a lower risk of periprosthetic infection in the corticosteroid cohort illustrating its mainstay usage in modern arthroplasty protocols that incorporate many approaches to minimize this devastating complication.

Although this is a prospective, double-blind, randomized, placebo-controlled trial and considered reasonably powered, there still exists potential limitations to the data. First, this study was only powered for patient VAS pain scores postoperatively and therefore the secondary findings should not be considered definitive and are subject to change when future studies are powered for such outcomes. While VAS and opioid usage are standard metrics in the pain literature, their applicability on a holistic approach to a patient's perception of pain control may be limited [31]. We were also unable to differentiate time discrete points based on activity such as before or after therapy which can introduce sampling bias. Also, due to the exclusion criteria, this study cannot draw the same conclusions to patient populations that were not included in the protocol, for example chronic pain patients on preoperative opioids, which stand as a group that could greatly benefit from multimodal pain medications. The power analysis and study occurred during enrollment and collection challenges made worse by the COVID-19 pandemic, so given different methods of power analysis this may have been underpowered to witness more substantial differences. The change in VAS was only a small difference as well, so clinical relevance beyond introductory safety of use and the potential for idealized dosages would need further evaluation in larger studies.

Conclusion

This prospective, double-blind, randomized, placebo-controlled trial demonstrated the use of oral dexamethasone reduces patient's postoperative pain scores. There are indications that this additional medication has little downside, as it was seen to be safe for use in the studied patient population with no increase in postoperative complications nor effects on patient sleep. Combined with prior IV dexamethasone studies illustrating effectiveness for pain control with an adequate safety profile, consideration of the addition of a short-term course of oral corticosteroids to augment multimodal pain control after joint arthroplasty may be beneficial. Larger scale studies will be needed to better ascertain the clinical effectiveness and dosing while monitoring for side effects and complications.

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