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The Median Effective Volume of Crystalloid in Preventing Hypotension in Patients Undergoing Cesarean Delivery with Spinal Anesthesia

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Summary: Xu S, Wu H, Zhao Q, Shen X, Guo X, Wang F – The Median Effective Volume of Crystalloid in Preventing Hypotension in Patients Undergoing Cesarean Delivery with Spinal Anesthesia.

Background and objectives: Spinal anesthesia-associated maternal hypotension in Cesarean delivery is the most frequent and troublesome complication, posing serious risks to mothers and compromising neonatal well-being. The effective volume of intravenous crystalloid as the preventive strategy in this context has not been estimated.

Methods: Eighty-five parturients with ASA physical status I/II undergoing elective Cesarean delivery were screened and 67 eligible women were assigned to receive pre-spinal crystalloid loading. Hyperbaric 0.5% bupivacaine 2 mL (10 mg) plus morphine 50 μg was given to all patients. The volume of crystalloid was determined by an up-and-down sequential method. The crystalloid was infused at a rate of 100-150 mL.min^{-1} prior to the spinal anesthetic injection. The initial volume of crystalloid was 5 mL.kg^{-1}. Volume-effect data were fitted to a sigmoidal maximum efficacy model and the median effective volume (EV_{50}) and corresponding 95% confidence interval (95% CI) were estimated using maximum likelihood estimation and logistic regression with Firth's correction.

Results: A total of 67 subjects completed the study and were analyzed. Twenty-eight (41.8%) patients developed hypotension with their systolic blood pressure (SBP) decreasing > 20% of baseline. The EV_{50} of crystalloid were 12.6 mL.kg^{-1} (95% CI, 11.6 to 14.8 mL.kg^{-1}). With Firth's correction, the pooled probability of an effective preventive volume of crystalloid at 13 mL.kg^{-1} was 50.2% (95% CI, 30% to 83.1%).

Conclusions: The estimated EV_{50} of the preloaded crystalloid required to prevent spinal anesthesia-induced hypotension in a Cesarean section is, approximately, 13 mL.kg^{-1}. However, prophylactic or therapeutic vasoconstrictors should also be prepared and administered at an appropriate time.

Keywords: Anesthesia, Spinal; Cesarean Section; Isotonic solutions; Hypotension/prevention and control.

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INTRODUCTION

Spinal anesthesia-associated maternal hypotension is the most frequent and troublesome complication resulting from sympathetic blockade that poses serious risks to the mother and compromises neonatal well-being [1-4]. Intravenous fluid management is now considered an acceptable means of preventing spinal anesthesia-induced hypotension, despite the fact that the choice of fluid type (crystalloid or colloid) [5-8], intervention timing (pre-, during or post-anesthesia loading) [9-12], titration speed (pressured-fast, fast or slow) [13,14] and volumes given (high or low) [15,16] are still debated and different choices have yielded different results.

Clinical guidelines recommend that intravenous fluid preloading should be used to reduce the risk of maternal hypotension after neuraxial anesthesia for Cesarean delivery, but no detailed strategies were given to achieve this [17,18]. A recent Cochrane systematic review showed an effectiveness sequence of fluids in reducing hypotension frequency of patients related to spinal anesthesia: colloids > crystalloids > no fluids. However, no differences were found for different doses, rates or methods of administering colloids or crystalloids [19], and the included studies did not calculate the effective volume of fluids under spinal block. Preloading the intravascular circulation is meant to generate the volume expansion that

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alleviates vasodilation induced by regional anesthesia. Nonetheless, the coloading or postloading regimen has been proposed due to a much more effective role in decreasing the rate of hypotension [9-12]. However, Banerjee et al. [20] reviewed on how the incidence of maternal hypotension in spinal anesthesia is still high - about 60% - regardless the fluid loading strategy used. In addition, neither of the conventional methods of fluid management - wether 'liberal' (2,000 mL per person) or 'restricted' (500 mL per person) - produced ideal effects on preventing hypotension and balancing circulation.

In our previous observation, the regimen of single fluid preloading in patients undergoing Cesarean section could not surpass 80% effectiveness in preventing spinal anesthesia-induced hypotension. In January 2008, we initiated a study to estimate the median effective volume (EV_{50}) of crystalloid in preventing hypotension associated with spinal anesthesia in parturients during cesarean through an up-down sequential allocation volume-escalation method.

METHODS

Participants and ethics

Ethical approval was obtained from the institution's Ethics Examining Committee of Human Research before recruiting patients. All participants signed an informed consent and a full explanation was given to those willing to accept spinal anesthesia with respect to lumbar spinal puncture, the opioid and local anesthetics used in this study, as well as possible risks and complications that could appear during study. Recruitment for this study took place between January and July 2008 at a tertiary teaching hospital in China. Screened-for-participating parturients were eligible if they would be undergoing elective Cesarean delivery, with aged between 19 and 40 years old, and fulfilled the following criteria: gestational age ≥ 36 wk, height > 140 cm or < 175 cm, American Society of Anesthesiologists (ASA) physical status I to II and uncomplicated singleton pregnancy.

Exclusion criteria

Parturients were excluded from the study if one or more of the following criteria were met: (1) multiple gestations; (2) allergy to local anesthetics or opioids; (3) a history of psychiatric diseases; (4) participants younger than 18 or older than 40 years; (5) those who were not willing to or could not finish the whole study; (6) primary hypertension, gestation-induced hypertension or preeclampsia/eclampsia; (7) emergency Cesarean section or parturients that have failed vaginal delivery with epidural analgesia; (8) contraindications for performing neuraxial anesthesia.

Demographic characteristics

The following data were collected as demographic characteristics of the subjects: age at delivery, weight, height, gestational age of fetus, current status of smoking, nulliparous or multiparous status and maternal vital signs (blood pressure, heart rate, respiratory rate and oral temperature).

Study procedures

Patients were given the initial volume of fluid: 5 mL.kg^{-1} of lactate Ringer's solution. This volume was chosen based on our clinical experience and statistical simulation at various doses from previous observation. Each subsequent volume relied on the response of the preceding subject following Dixon's up-and-down biased coin design sequential method [21,22]. The changing volume of the fluid was in an increment of 1 mL.kg^{-1}. All women who encountered hypotension were prescribed a repeatable ephedrine 6-10 mg intravenously. If a successful prevention was observed, the next parturient was assigned to the next lower volume with a probability of 0.1 and to the same volume with a probability of 0.9 as described elsewhere [23]. We set the infusion rate of the fluid to 100-150 mL.min^{-1} for all subjects. Lactate Ringer's solution at a titrating rate of 10 mL.min^{-1} was followed after completion of all interventional fluid regimens and the total volume was calculated at the end of the surgery.

All women received spinal anesthesia at levels between L3 and L4 interspace while in the left-lateral jackknife position using hyperbaric 0.5% bupivacaine 2 mL (10 mg) plus morphine 50 μg. After completing the anesthetic procedure, patients were immediately repositioned to supine with a 15°-30° left lateral tilt. The highest sensory block was checked and confirmed at the level of T3-T5 determined with loss-to-pinprick method bilaterally at 5 minutes and 10 minutes after spinal drug administration. Motor block was measured with modified Bromage scale (0, no block; 1, inability to raise extended leg; 2, inability to flex knee; 3, inability to flex ankle and foot).

After the anesthetic procedures were completed, arterial blood pressure was measured every minute for 20 minutes and then every 3 minutes for the duration of the study. In our study, hypotension was defined as the reduction of systolic blood pressure (SBP) > 20% of baseline. Baseline arterial blood pressure was determined measuring the patient's arterial pressure three times every 5 minutes at supine position with left uterine displacement one day before entering into operating theater.

Peripartum management and monitoring

A catheter was inserted in a right or left antecubital vein for fluid and drug administration. The maternal parameters monitored during the whole study included the heart rate by three-lead electrocardiograph, respiratory rate, noninvasive systolic and diastolic blood pressure, mean arterial pressure, oral temperature and fingertip pulse oximetry. Ondansetron 4 mg can be administered intravenously if nausea or vomiting persisted, even when hypotension had been corrected. After delivery of the baby, 20 IU of oxytocin was titrated following lactate Ringer's solution.

Statistical analysis

Statistical analyses were done using GraphPad Prism version 5.0 (GraphPad Software, Inc., San Diego, CA) or SPSS version 13.0 (SPSS Inc., Chicago, IL). Values are expressed as

the mean, standard deviation (SD), interquartile range (IQR), or numbers. All statistical tests were two-sided and the statistical significance was accepted at the level of $p \leq 0.05$. All categorical data were analyzed with a chi-square test or Fisher's exact test (as appropriate). The difference in parametric data was compared with the Student t-test. The Mann-Whitney U test was used for non-Gaussian distributed variables and presented as the medians and IQRs. Volume-effect data were fitted to a sigmoidal maximum efficacy model by means of GraphPad Prism software. The EV_{50} and corresponding 95% CI was calculated using maximum likelihood estimation (MLE) and logistic regression with Firth's correction.

RESULTS

Eighty-five parturients were screened for eligibility and 16 subjects were excluded before informed consent because of the reasons shown in Figure 1. Two patients declined to participate after signing the informed consent. Finally, 67 subjects completed the study and were analyzed.

Table I summarizes the demographic, background characteristics, baseline vital signs (all were within the physiologic range), and surgical and anesthetic variables. No statistical difference was observed on these variables between those who experienced hypotension and those not.

Subjects that developed hypotension per study protocol are presented in Table II. The patient flow of crystalloid preloading at different volumes with failure of hypotension prevention is presented in Figure 2. The median time of fluid administration was 6.5 minutes (IQR, 4.3 to 8.1 min). A total of 28 patients (41.8%) experienced hypotension and the median reduction in SBP was 23% (IQR, 21% to 26%) from the baseline. The ephedrine dose prescribed for hypotension was 10 ± 4 mg. The median time from spinal anesthetic administration to hypotension was 5.8 minutes (IQR, 4.2 to 9.7 min). Calculated with the MLE of the observed data, the EV_{50} of preloading crystalloid for preventing spinal anesthesia-induced hypotension was 12.6 $mL.kg^{-1}$ (95% CI, 11.6-14.8 $mL.kg^{-1}$) (Figure 3). Figure 4 shows the pooled probability of an effective response to preloading crystalloid corrected with Firth regression, and the probability at 13 $mL.kg^{-1}$ was 50.2% (95% CI, 30.0% to 83.1%).

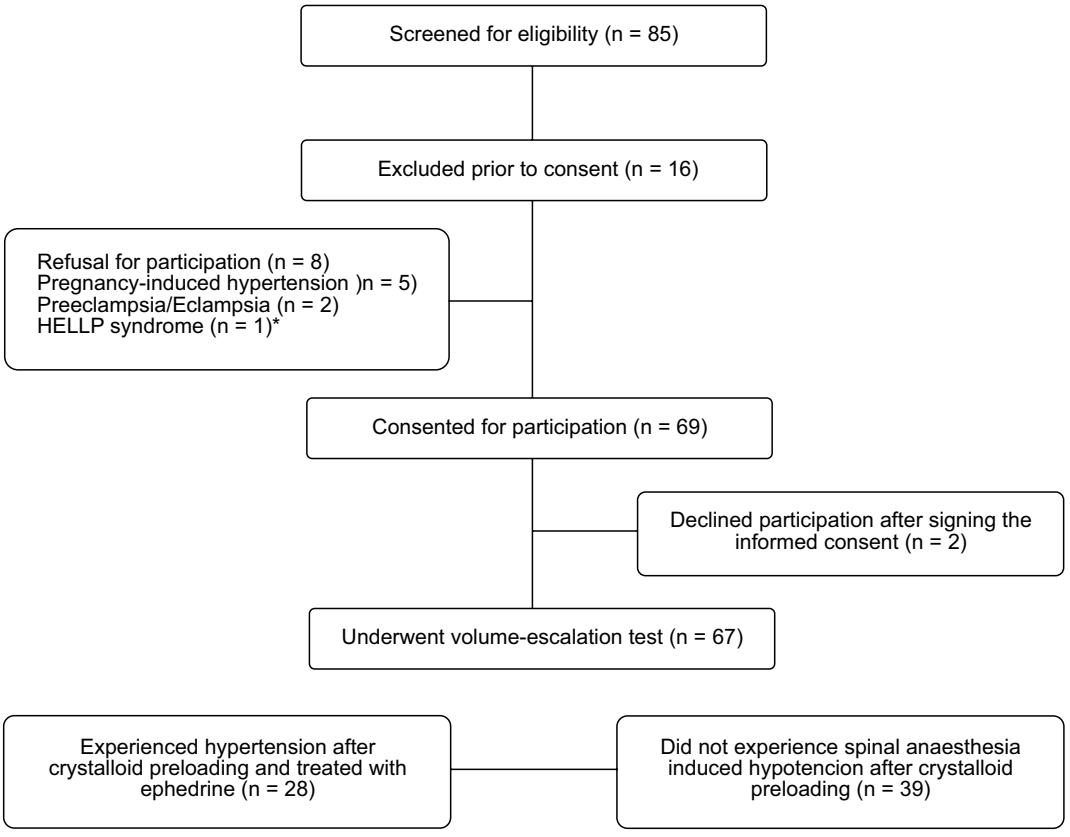

Figure 1 – Flow Chart of the Subjects.
* HELLP syndrome refers to hemolysis, elevated liver enzyme and low platelets syndrome

Table I – Demographic Characteristics, Anesthetic and Surgical Data of Subjects*

Variable	Hypotension Patients (n = 28)	Nonhypotension Patients (n = 39)
Age at delivery, yr	26 ± 6	27 ± 6
Weight, kg	61 ± 10	60 ± 11
Height, cm	161 ± 11	158 ± 9
Nullipara, n	24 (85.7)	35 (89.7)
Gestational age, wk	38 (37 – 40)	39 (38 – 40)
Blood pressure, mm Hg		
Systolic pressure	117 ± 13	111 ± 15
Diastolic pressure	70 ± 6	68 ± 5
Heart rate, bpm	77 ± 12	74 ± 11
Respiratory rate, bpm	17 ± 2	16 ± 2
Oral temperature, °C	36.7 ± 0.4	36.5 ± 0.3
Sensory block level at 5 min	T4 (T3 – T4)	T3 (T3 – T5)
Sensory block level at 10 min	T3 (T3 – T4)	T3 (T3 – T4)
Duration of surgery, min	46 (40 – 58)	50 (44 – 67)
Estimated blood loss, mL	420 (390 – 550)	450 (380 – 570)
Additional fluid volume, mL	560 (510 – 660)	520 (490 – 680)

No statistically significant difference between hypotensive and nonhypotensive patients.
* Data are presented as the mean ± standard deviation (SD), median (interquartile range, IQR) or number (%), unless otherwise indicated.
(bmp): beats per minute of heart rate and breaths per minute of respiratory rate.

Table II – Data Estimated with Isotonic Regression and Pooled-Adjacent-Violators Algorithm

Volume (mL.kg-1)	Effective (n)	Tested (n)	Probability (Raw)	Probability (Pooled)
5	0	1	0	0
6	0	1	0	0
7	0	1	0	0
8	0	2	0	0
9	1	3	0.33	0.33
10	1	3	0.33	0.37
11	1	3	0.33	0.37
12	2	4	0.50	0.48
13	6	9	0.67	0.56
14	4	6	0.67	0.56
15	4	6	0.67	0.58
16	5	8	0.63	0.65
17	5	7	0.71	0.65
18	5	7	0.71	0.70
19	3	4	0.75	0.86
20	2	2	1.00	1.00

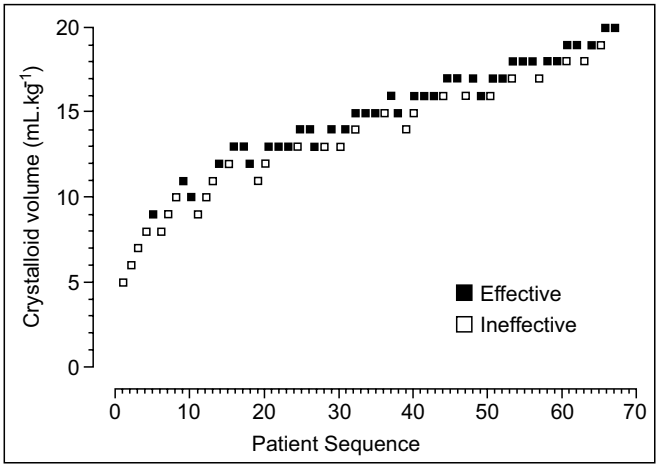

Figure 2 – Patients' Up-down Sequential Schema.
Frequencies of volumes of preloading crystalloid, patients' responses, and subsequent volume allocation.

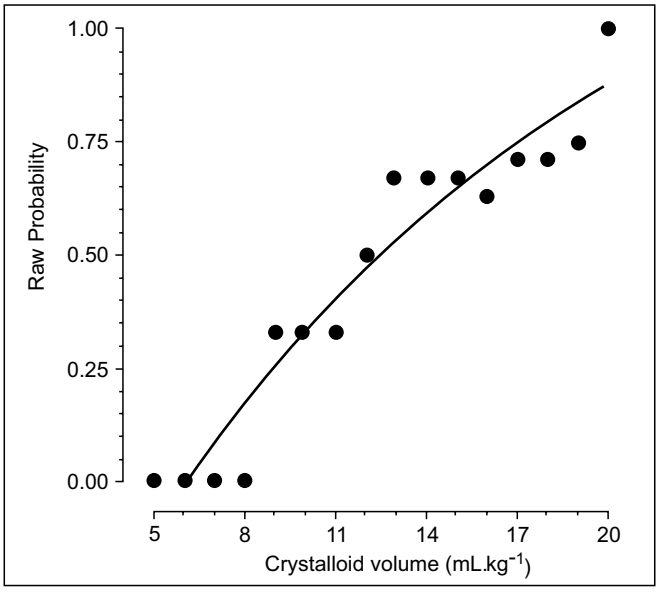

Figure 3 – Raw Probabilities.
Effective responses of preloading crystalloid volumes determined with logistic regression and maximum likelihood estimation (MLE) of the observed data.

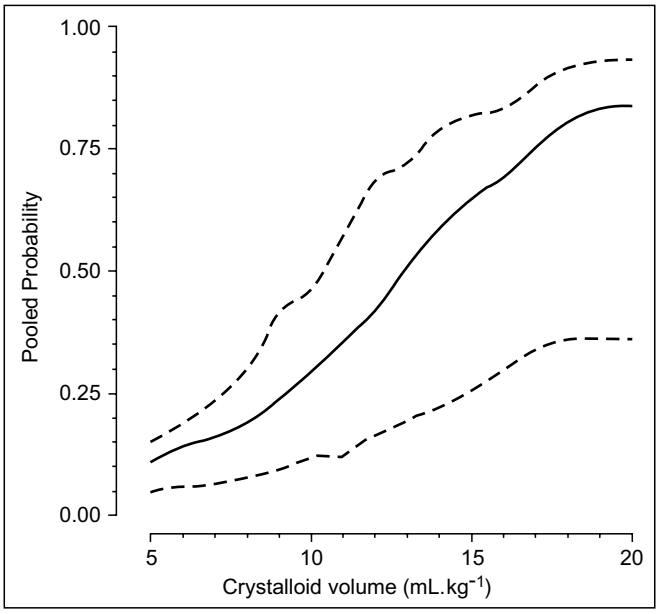

Figure 4 – Pooled Probabilities.
Effective responses of preloading crystalloid volumes determined using Firth's regression with corresponding 95% confidence intervals (95% CI).

DISCUSSION

In our study, we estimated that the EV_{50} of crystalloid required to prevent hypotension induced by spinal anesthesia in patients undergoing Cesarean delivery is 13 mL.kg^{-1} when the fluid was given prior to anesthesia. To our knowledge, this is the first study to determine the effective volume of preloading crystalloid spinal anesthesia in parturients during cesarean through an up-down sequential allocation. The result is consistent with what is typically reported in clinical use that 500-1,000 mL of crystalloid should be preloaded before anesthesia induction.

Fluid given to prevent spinal anesthesia-induced hypotension in Cesarean section has been discussed for decades [9-12,24], but the precise volumes have still not been reached. Those who praise the 'liberal' fluid therapy suggested that increase in blood volume with preloading must be large enough to result in a significant improved cardiac output for the effective prevention of hypotension and, in their studies, at least 1,500-2,000 mL crystalloid was recommended [5,6]. Nevertheless, the 'restricted' supporters considered that extreme expansion of the blood volume with prophylactic fluids would exert negative effects on maternal and infant outcomes, thus they proposed a relatively lower volume of fluids: 1,000 mL of crystalloid was commended [24-26]. However, several studies disapproved the fluid-loading regimen because no significant difference has been found with any given volume of fluid infused [11,16,27]. In Banerjee's systematic review, approximately 60% of patients still developed hypotension in both preloading and coloading regimens [20]. In our study, we observed about 42% of patients experience hypotension and the EV_{50} of crystalloid was 13 mL.kg^{-1}. This difference suggests that a further evaluation on this issue is warranted in a different racial population.

Preloading regimen of fluid is recommended for its prophylactic role of hypotension through prior augmentation of the circulation, but more recent studies displayed similar effect of coloading and postloading maneuvers [10,11]. Williamson and others suggested the combined method of preloading and coloading should be used as a substitute for the simple preloading crystalloid fluid administration [12]. Dyer and colleagues considered that the timing of fluid administration is the reason for ineffectiveness of the traditional preloading method for a period of fluid titration over 20 minutes prior to anesthesia induction, and they emphasized using a rapid crystalloid infusion after spinal anesthesia [14]. In our study, the targeted volumes of crystalloid were given with a rate of 100-150 mL.min^{-1}, which guaranteed a rapid infusion of the fluid to a median time of fluid administration of 6.3 minutes. Nonetheless, the high rate of hypotension - about 42% - suggests that preloading crystalloid is not an absolutely effective means for hypotension prevention in spinal anesthesia. In addition, six women experienced recurrence of hypotension despite ephedrine being prescribed. Interestingly, these six people received 5-8 mL.kg^{-1} fluid. This suggests that they likely required a higher volume than what was allocated in the study.

The method of up-and-down sequential allocation is usually used to determine the effective doses of drugs in pharmacology. In our study, we adapted it to estimate the median effective fluid volume using isotonic regression and pooled-adjacent-violators algorithm. Although the 90% effective volume (EV_{90}) might be more clinically useful, the study context itself restricted us to do so. We attempted to estimate the

EV_{90} of crystalloid but failed because preloading fluid alone cannot successfully prevent or reverse hypotension in spinal anesthesia- related Cesarean section patients. Given that the natural unpredictability of timing and degree of hypotension resulting from spinal anesthesia for Cesarean section, we only reported the EV_{50} of preloading crystalloid, which displays a relatively wider precision than that of the EV_{90}.

Neonatal outcomes are a major consideration for Cesarean parturients under neuraxial anesthesia due to the threat from hypotension. However, recent literatures show that despite the high prevalence of maternal hypotension, term infants can tolerate this placental blood perfusion challenge without any major negative consequences [28]. Meanwhile, a range of studies also have not found any sequel from the fluid interventions in patients undergoing Cesarean section with neuraxial blockade [27,29,30]. Our results are consistent with these findings, where fluid preloading produced little effect on infants' Apgar and neurobehavioral assessment scorings, as well as on the arterial umbilical-cord pH values.

The present study has several limitations. Firstly, although the dosage should generally traverse the ED_{50} estimate by five crossings during the up-down sequential allocation in order to be robust, we used a 1 $mL.kg^{-1}$ fluid's interval to estimate the EV_{50} of preloading fluid. Thus, there were 21 crossings from 5 to 20 $mL.kg^{-1}$ for the probability calculation. How this affects the final results is unknown. Secondly, we did not observe the effect of the fluid volumes over 20 $mL.kg^{-1}$, so this fact should taken into account when the probabilities estimated with the MLE and the Firth's correction were introduced to other populations.

In summary, the estimated EV_{50} of preloading crystalloid for the prevention of spinal anesthesia-induced hypotension for Cesarean section is approximately 13 $mL.kg^{-1}$. These data are concordant with other previous reports that large amount of fluids are not necessarily useful in balancing maternal hemodynamics.[15] While preloading fluid can reduce the rate of spinal anesthesia-induced hypotension, it cannot totally eliminate the occurrence with a rate of 40% or more. Therefore, at the time of fluid loading, prophylactic or therapeutic vasopressors should also be prepared and administered at an appropriate time, since a significant proportion of parturients can still develop hypotension.

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