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A PROSPECTIVE, RANDOMIZED, CONTROLLED, TRIPLE-BLINDED, SINGLE CENTRE TRIALEVALUATING THE POSTOPERATIVE ANALGESIC EFFECT OF BUTORPHANOL AS ADJUVANT TO 0.25% BUPIVACAINE COMPARED TO 0.25% BUPIVACAINE ALONE IN CAUDAL EPIDURAL IN ADULT PATIENTS UNDERGOING SINGLE-LEVEL LUMBAR DISC SURGERIES

Anaesthesiology

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ABSTRACT

Introduction- Patients undergoing Lumbar Laminectomy experience severe postoperative pain increasing morbidity. Optimal pre-emptive pain relief hastens rehabilitation, and decreases incidence of chronic pain. Prone position and fluoroscopy guidance used for Spine surgeries is ideal for the application of caudal epidural block. Use of Butorphanol to prolong analgesia in Spine patients is lacking in the literature. Hence, this study was put into effect.

Methods-After block randomization, 60 ASA grade I and II adult patients were allocated to 2 groups- Group A- received 20 ml of 0.25% Bupivacaine in the Caudal Epidural Space, Group B- received 20 ml of 0.25% Bupivacaine to which 25 micr/kg of Butorphanol was added in the Caudal Epidural Space. The primary outcome was to study the postoperative analgesic duration, secondary outcome was comparison of the perioperative hemodynamics between the two groups.Student t-test (two-tailed, independent), Chi-square/ Fisher Exact Test were used as tests of significance for intergroup analysis and categorical data respectively.

Results-The mean time for the demand of rescue analgesic was 6.33+-3.09 hrs in Group A vs 11.20 +-4.38 hrs in Group B. The mean total 24 hour analgesic consumption was 79.0+-20.06 mg in Group A vs 44.0 +-15.22 mg in Group B. The differences were statistically significant. Also, Group B was hemodynamically more settled compared to Group A in 24 hours postoperatively.

Conclusion-Pre-emptive Butorphanol (25 micr/kg) addition effectively prolongs the analgesic duration of 0.25% Bupivacaine compared to Bupivacaine alone administered in Caudal epidurals for Single-level Adult Lumbar Spine Surgeries. The combination also gives more hemodynamic stability for 24 hrs postoperatively.

KEYWORDS

Butorphanol, Bupivacaine, Caudal, Epidural, Postoperative pain

Introduction

Patients undergoing lumbar laminectomy experience severe pain in the postoperative period, which may increase the incidence of postoperative morbidity and complications. Adequate pain relief hastens rehabilitation, and the incidence of its conversion into chronic pain is decreased. Preemptive analgesia describes the concept of decreasing pain perception and overall analgesic need by use of a drug regimen capable of inhibiting CNS sensitization before the application of painful stimuli[1].Various techniques have been utilized to provide preemptive analgesia including the administration of medications through the oral, intravenous and neuraxial routes[2,3].

Prone position of the patient along with the ready availability of image intensifier is an ideal setting for the caudal epidural block[4,5,6] in patients undergoing lumbar spine surgeries.

The efficacy of caudal bupivacaine and butorphanol as preemptive analgesics has been compared predominantly in pediatric patients or animals[7,8,9]. However to our knowledge, the use of similar combinations in adult lumbar spine surgery are lacking. We, therefore, decided to conduct the following study to evaluate the role of butorphanol as an additive to bupivacaine in adult lumbar spine surgeries. We hypothesized that there is no difference between postoperative analgesia produced by Epidural administration of Bupivacaine with or without Butorphanol use.

Methods

The trial was designed as a randomized, controlled, patient, observer and surgeon blinded, single center trial to evaluate the efficacy of Butorphanol as adjuvant of bupivacaine in prolonging the analgesic effect. The study period was June 2012 to 2015. Based on previous study9using the expected differences in means, with 95% confidence interval and 90% power, the minimum sample size was calculated as 28 in each group. We included 30 patients having L5 S1 disc disease in each group during the period of our study.

After approval from the Institutional ethics committee, 60 ASA grade I and II patients scheduled for single level lumbar disc prolapse surgery were randomized into two groups as follows:

Group A (Bupivacaine): Thirty patients received single caudal injection of 20 ml of 0.25% bupivacaine before the incision Group B (Butorphanol +Bupivacaine): Thirty patients received single caudal injection of 20 ml of 0.25% bupivacaine with 25 microgram/kg of Butorphanol before the incision.

Patients refusing consent, ASA grade III and IV patients and patients with with co-morbid conditions like uncontrolled Diabetes Mellitus, Cardiovascular Diseases, Renal, Hepatic disorders, coagulopathies and infections, known allergies to any drugs and pregnancy were excluded.

Randomization was performed by block randomization using a computer-generated sequence of random numbers in block sizes ranging from 2-8, with a 1:1 allocation. A statistician who was not a part of the research team generated the random allocation sequence.

Written, informed consent of the procedure was taken from the patients who met the inclusion criteria. After overnight fasting, all patients were premedicated with Tab. Diazepam 7.5 mg with few sips of water 90 minutes before induction of anaesthesia. On arrival to the operation theater, an 18 Gauge Intravenous cannula was inserted and preloading with Ringer Lactate was done at 10 ml/kg. Patients were monitored using a standard Anaesthesia monitor for Electrocardiogram, Non-Invasive Blood Pressure, Heart Rate, and Pulse oximetry in the preoperative period.

All patients were anaesthetized with standard technique consisting fentanyl 2 micrograms/kg, Thiopentone sodium 5-6 mg/kg and Pancuronium 0.1 mg/kg body weight. Preservative free Xylocaine 1.5mg/kg was given to attenuate the pressor response to intubation.

Maintenance was carried with O2 and N2O in a ratio of 33:67 and Isoflurane 1%. Tidal volume of 6-8 ml/kg and ventilatory frequency of 10-15 breaths/min were adjusted to maintain normal EtCO2 levels.

Patients were placed in prone position on Wilson's frame and sacral hiatus identified. A bolster was placed underneath the pelvis so as to improve the visualization of the caudal epidural space. Once in the prone position, the patient was prepared for administration of Caudal epidural analgesia, the sealed envelope containing the randomization sequence was opened by the theatre floor nurse (not a part of the research team) and based on the allocation (group A or B), the drugs were prepared by the another nurse (also not a part of the research team). Hemodynamic parameters (HR, NIBP, SpO2)were noted before application of caudal block. After sterile skin preparation and draping with sterile towels, Tuohy's 18G epidural needle was advanced at 45 degrees angle cephalad until pop was felt as needle pierces sacrococcygeal ligament. Angle of needle was then flattened and advanced. Epidural space was confirmed with loss of resistance technique. Negative aspiration for either CSF or blood was confirmed before the block. Placement of the Tuohy's needle in caudal space was confirmed with image intensifier using a water-soluble, iodine-based contrast agent. Caudal block with 20 ml of 0.25% bupivacaine (group A) or bupivacaine along with 25 microgram/kg of Butorphanol (group B) was given 20 minutes before skin incision. Hemodynamic parameters were mentioned after the block at 5,10,15, 20, 25, 30, 40, 50, 60, 75, 90 and 120 min.

At the end of surgery the neuromuscular block was antagonized with intravenous neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. After tracheal extubation, the patients were transferred to postoperative ICU. Continuous monitoring of pulse rate, blood pressure, SpO2, ECG and respiratory rate was done in ICU for 12hrs after surgery and later shifted to ward where regular monitoring of pulse rate, blood pressure and respiratory rate was done every 2 hours for next 12 hours. Patients were assessed for all possible complications after caudal block like bradycardia, hypotension, respiratory depression, cardiac arrhythmias, urinary retention, CNS toxicity, lower limb weakness and total spinal anaesthesia. Postoperative pain and weakness/sensory deficits in lower limbs were assessed once the patient had completely recovered from general anaesthesia. Anaesthesia staff blinded to the allocated group did Assessment.

Assessment of postoperative pain based on visual analogue scale [0 = no pain and 10 = worst pain imaginable] was done hourly for the first 4 hours and 4 hourly after that till 24 hours after surgery.

Postoperative analgesic Inj. Ketorolac 30 mg was given as a rescue analgesic only if the pain score on visual analogue scale was more than 4. The time duration for the first demand for rescue analgesic was noted along with total requirement of analgesic during 24 hours after surgery. Statistics The primary objective of the study was to study the analgesic prolongation of 25 mic/kg Butorphanol with 20ml of 0.25% Bupivacaine vs. 20 ml of 0.25% Bupivacaine alone administered in the caudal epidural space in adult patients undergoing Single-level Lumbar Disc Surgeries. The secondary objectives were to study the hemodynamic changes and incidence of complications after pre-incisional single caudal epidural injection of either Bupivacaine or Bupivacaine with Butorphanol in patients undergoing surgeries on the Lumbar Spine.

The pre-caudal, post- caudal and postoperative data (HR, Systolic BP, Diastolic BP, Mean BP, SpO2, Duration of Surgery) was subjected to student t-test, results of which were presented on Mean+-SD (min-max). The test used for data on postoperative analgesic requirement and postoperative VAS was Student t-test and data expressed as Mean +-SD. Data on the number of patients demanding rescue analgesia was evaluated aby Chi- Square test. Significance was assessed at 5 % level of significance.

Student t test (two tailed, independent) was utilized to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test was the test of significance of study parameters on categorical scale between two or more groups.

The Statistical software used were SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results-

This study was carried out on a total number of 60 patients who underwent surgery for prolapsed lumbar disc (PIVD). The participant flow diagram is depicted in Fig.1. The study was carried out between June 2012 and January 2015. Demographic data, Duration of surgeries, Baseline and pre-procedure hemodynamic parameters (HR, SBP, DBP) and baseline oxygen saturation were comparable and are given in Table 1.The mean heart rates before and after the caudal block at 5, 10, 15, 20, 25, 30, 40, 50,60 and 75 minutes intraoperative were comparable (Table 1). Mean heart rates in postoperative period were comparable at 1/2 ,1 ,2 ,3 ,4 ,8 ,12 and 20 hours in both the groups but at 16 and 24 hours, the mean heart rate was statistically more in group A (81.73+-4.16 bpm)and (81.17+-3.90) than that in group B (80.00 +-2.99 bpm) and 80.47+-3.33 bpm respectively (Table 2). Mean systolic and diastolic pressures before and after the caudal block were comparable but these were significantly lower normal over 24 hours postoperatively in Group B compared to A, systolic pressures were 121.37+-7.22 mm Hg in group A and 118.07 +-7.08mm Hg in Group B and diastolic blood pressures were 78.77+-6.53 in group A and 75.37 +_6.78 (Table 3,4,5,6). Mean Arterial pressures were significantly lower at 24 hours 89.57 +-6.51 in group B than 93.07 +_6.11 in Group A(Fig 2). Mean Oxygen saturation before, after the block and postoperatively were comparable (Table 7). There was a statistically significant difference in the mean VAS scores at 1, 2, 3, 4, 8, 12, 16, 20 and 24 hours after the application of the block in Group B vs Group A, the data is tabulated in the Table 8There was a statistically significant difference in the time for demanding the first dose of rescue analgesic in Group B (11.20+-4.38 hrs) vs. Group A (6.33+-3.09 hrs) (Table 9) (Fig 3).The total analgesic consumption in 24 hours was significantly lesser in Group B (44.00+-15.22) mg vs Group A (79.00+-20.06 mg) (Table 10). Complications such as motor block, bradycardia, hypotension, cardiac arrythmias, respiratory depression, and urinary retention were not seen in either of the groups within 24 hours after the block.

Discussion-

Woolf first described the use of pre-emptive analgesia to reduce the magnitude and duration of postoperative pain in 1983[10]
Use of epidural route for pre-emptive analgesia has been widely studied in pediatric population[11,12,13,14], however there is a paucity of literature regarding use of epidural analgesia in adult patients.

Bupivacaine when used alone through caudal route has the limitation of brief duration of action for postoperative analgesia. To prolong the duration of single shot caudal analgesia and to decrease the doses of the individual drugs, many adjuvants have been administered along with bupivacaine eg. Morphine, clonidine, tramadol, ketamine, neostigmine and Butorphanol [15,16].

Our study shows that in comparable groups, the addition of 25 mic/kg of Butorphanol to 0.25% Bupivacaine in Caudal block gives better postoperative analgesia, in terms of demand for first rescue analgesic and total 24 hour analgesic requirement, in patients posted for spine surgeries compared to 0.25% Bupivacaine alone. The patients, in whom Butorphanol was used as an adjuvant, were hemodynamically more settled postoperatively, than those in whom Butorphanol was not used as an adjunct, when Heart Rate, Systolic, Diastolic and Mean Arterial pressures were observed. No postoperative motor block, bradycardia, cardiac dysrrhythmias, respiratory depression, urinary retention were noted.

The reason behind the prolongation of postoperative analgesia may be because of the synergistic action of opioids (Butorphanol) with Local Anaesthetic(Bupivacaine). Several studies support our finding. Studies done by Veena Chatrath et al[17], Vinita Singh et al[18] and Neerja Bharti et al[19] have shown prolongation of postoperative analgesia on using Butorphanol as an adjuvant to either 0.25% or 0.125% of Bupivacaine.

Comparable results were also reported by Abdelfattah Saoud et al[20],they observed that Pre-emptive caudal bupivacaine morphine in single level lumbar decompression and instrumented posterolateral inter transverse fusion surgery provided prolonged postoperative duration of analgesia with less analgesic requirements of NSAIDs and pethidine in both intra and postoperative periods. Patients were ambulated earlier without occurrence of any hemodynamic changes or increased incidence of adverse effects.

There are certain limitations in our study- First, our sample size was small. Further large sample size studies are required to substantiate our findings. Second, the study was done only on the ASA grade I and II patients, so the efficacy and side effects of Butorphanol in patients with innate cardiovascular compromise could not be studied well. Third, postoperative pain was measured using VAS scores, which is a subjective criterion for assessing pain, objective criteria like biochemical markers complimentary to subjective assessment improve the validity of the assessment.

Conclusion-

It is concluded that 25 micr/kg Butorphanol addition to caudal administration of 20 ml of 0.25% bupivacaine, is an effective means for prolonging the duration of postoperative analgesia of 20 ml 0.25% Bupivacaine in adult patients undergoing Lumbar PIVD surgeries in terms of increased quality and duration of analgesia without any hemodynamic instability or any increased incidence of side effects. Further studies however, may be required to validate our findings.

Table 1- Baseline Demographic and Hemodynamic Parameters

Baseline Demographic and hemodynamic parameters			
Parameters	Group A	Group B	P value
Age (years), Mean	40.53 +-7.12	42.33+-5.59	0.249
Gender (M/F),%	66.7/33.3	63.3/36.7	1.000
Weight (kgs) mean +- S.D.	57.73+-9.38	60.37+-9.63	0.508
Height (cms) Mean +-SD	160.43+-6.54	159.90+-8.76	0.790
Duration of Surgery (min) Mean+-SD	77.69+-15.95	75.00+-16.56	0.528
Baseline heart rates	81.90+-6.76	81.70+-8.94	0.922
Mean Heart Rates Before the caudal block	91.67+-5.62	91.97+-8.14	0.869
Baseline systolic BP	120.13+-9.15	120.33+-8.03	0.929
Systolic BP before Caudal Block	121.77+-12.22	123.37+-8.47	0.588
Baseline Diastolic BP	83.53+-6.12	84.27+-5.01	0.614
Diastolic BP before caudal block	84.93+-9.57	86.47+-5.92	0.459
Baseline Mean arterial BP	95.80+-6.80	96.23+-5.05	0.780
Mean Arterial Pressure before caudal block	97.23+-10.24	98.77+-6.48	0.491
Baseline O2 saturation	98.57+-0.97	98.27+-1.05	0.255

Table 2 :Mean heart rates in post operative period

		Mean heart rate (bpm) (Mean+SD)		P value
		Group A	Group B	
Baseline	81.90±6.76	81.70±8.94	0.922	
Duration after surgery (post operative period)	30min	84.50±5.12	83.6±3.61	0.435
	1hr	82.40±4.55	81.5±3.32	0.385
	2hr	81.60±4.30	80.08±3.24	0.419
	3hr	81.43±3.98	80±3.11	0.125
	4hr	81.30±4.24	80.37±3.19	0.339
	8hr	81.07±4.03	79.8±3.12	0.179
	12hr	80.67±4.65	79.97±3.5	0.513
	16hr	81.73±4.16	80.00±2.99	0.069+
	20hr	81.17±3.90	80.47±3.33	0.457
	24hr	82.17±4.08	80.50±3.56	0.097+

Table 3: Mean systolic blood pressures before and after caudal block

		Mean systolic blood pressure (mm Hg) (Mean+SD)		P value
		Group A	Group B	
Baseline	120.13±9.15	120.33±8.03	0.929	
Before caudal block	121.77±12.22	123.37±8.47	0.558	
Duration (in minutes) after caudal block	5min	111.43±7.97	111.67±5.14	0.893
	10 min	104.97±7.94	106.00±5.17	0.552
	15 min	102.93±8.53	102.53±5.87	0.833
	20 min	102.27±8.60	102.97±5.70	0.712
	25min	103.27±9.09	101.83±5.94	0.473
	30 min	102.97±9.24	101.90±7.71	0.629
	40 min	102.7±9.22	101.70±7.43	0.645
	50 min	104.6±8.21	104.73±7.11	0.947
	60 min	103.48±8.58	104.07±8.09	0.792
	75 min	101.70±9.17	103.50±7.82	0.482
	90 min	106.33±8.29	107.33±4.46	0.793
	120 min	102.00±11.31	107.00±7.07	0.649

Table 4:Mean systolic blood pressures in post operative period

		Systolic blood pressure (mm Hg) (Mean+SD)		P value
Baseline	120.13±9.15	Group A	Group B	0.929
Duration after surgery (post operative period)	30min	118.63±12.98	116.57±10.51	0.501
	1hr	119.07±12.19	116.07±11.22	0.325
	2hr	116.17±10.3	114.10±10.62	0.447
	3hr	117.57±11.42	113.73±12.02	0.210
	4hr	117.37±10.68	118.27±11.29	0.752
	8hr	117.10±11.93	120.67±12.14	0.256
	12hr	118.63±12.87	119.43±11.00	0.797
	16hr	121.70±9.59	120.33±7.61	0.543
	20hr	120.13±8.39	119.47±7.23	0.743
	24hr	121.37±7.22	118.07±7.08	0.079+

Table 5:Mean diastolic blood pressures before and after caudal block

		Diastolic blood pressure (mm Hg) (Mean+SD)		P value
		Group A	Group B	
Baseline		83.53±6.12	84.27±5.01	
Before caudal block	84.93±9.57	86.47±5.92	0.459	0.614
Duration (in minutes) after caudal block	5min	77.57±7.87	79.40±4.02	0.261
	10 min	74.23±7.26	75.47±4.09	0.421
	15 min	72.30±8.30	72.20±5.63	0.957
	20 min	71.20±8.45	71.07±5.85	0.944
	25min	71.77±9.13	71.87±6.73	0.962
	30 min	72.47±9.17	72.90±7.92	0.845
	40 min	71.67±7.90	71.83±7.55	0.934
	50 min	73.90±8.22	74.83±8.16	0.661
	60 min	72.76±7.52	75.56±7.55	0.171
	75 min	71.74±8.62	75.05±7.94	0.189
	90 min	75.11±11.05	76.50±5.28	0.781
	120 min	70.00±14.14	75.50±4.95	0.655

Table 6: Mean diastolic blood pressures in post operative period

		Diastolic blood pressure (mm Hg) (Mean+SD)		P value
		Group A	Group B	
Baseline		83.53±6.12	84.27±5.01	0.614
Duration after surgery (post operative period)	30min	79.60±10.61	76.77±9.82	0.288
	1hr	78.33±10.53	76.63±9.03	0.505
	2hr	76.27±8.00	73.57±8.54	0.211
	3hr	77.17±9.94	73.20±9.29	0.116
	4hr	76.60±9.31	76.57±8.17	0.988
	8hr	76.07±10.31	78.33±10.93	0.412
	12hr	78.20±10.99	77.63±9.33	0.830
	16hr	79.03±8.36	77.77±7.07	0.529
	20hr	76.53±8.14	75.63±7.23	0.652
	24hr	78.77±6.53	75.37±6.78	0.053+

Table 7: Comparative evaluation of Baseline and postoperative SpO2

		O2Saturation (Mean+SD)		P value
		Group A	Group B	
Baseline		98.57±0.97	98.27±1.05	0.255
Duration after surgery (post operative period)	30min	99.63±0.67	99.63±0.69	1.000
	1hr	99.53±0.73	99.62±0.67	0.337
	2hr	99.63±0.61	99.7±0.56	0.362
	3hr	99.60±0.67	99.67±0.60	0.395
	4hr	99.57±0.73	99.67±0.60	0.200
	8hr	99.60±0.67	99.62±0.69	0.854
	12hr	99.60±0.67	99.62±0.67	0.848
	16hr	99.60±0.62	99.63±0.64	0.689
	20hr	99.63±0.61	99.63±0.66	1.000
	24hr	99.53±0.73	99.60±0.67	0.445

Table 8: Postoperative VAS

	GP	N	Mean	Std. Deviation	P value
VAS2hr	1	30	2.77	.504	0.00
	2	30	2.23	.430	
VAS3hr	1	30	2.80	.714	0.001
	2	30	2.27	.450	
VAS4hr	1	30	3.33	.661	0.000
	2	30	2.50	.630	
VAS8hr	1	30	3.40	.498	0.005
	2	30	2.80	.997	
VAS12hr	1	30	3.53	.571	0.002
	2	30	2.87	.973	
VAS16hr	1	30	3.37	.669	0.005
	2	30	2.83	.747	
VAS20hr	1	30	3.33	.547	0.006
	2	30	2.83	.791	
VAS24hr	1	30	3.50	.509	0.002
	2	30	2.97	.718	

Table 9 : Time for First Demand of Rescue Analgesic

Duration after surgery	Number and % of patients requiring first dose of rescue analgesic				P value
	Group A		Group B		
	No	%	No	%	
1-2 hrs	1	3.3	0	0	
3-4 hrs	14	46.7	2	6.7	
5-8 hrs	11	36.7	12	40	
> 10hrs	4	13.3	16	53.3	
Mean ± SD	6.33±3.09 hrs		11.20±4.38 hrs		<0.001**

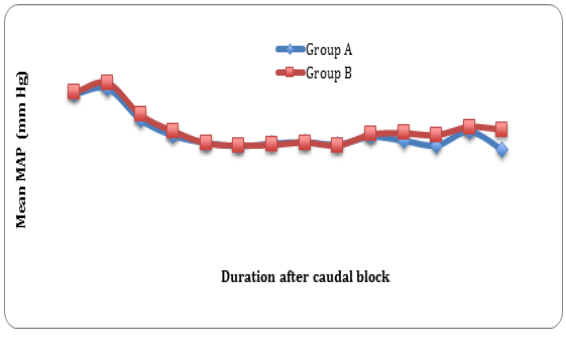

Figure 2: Graph comparing the Mean Arterial Pressure in both the groups

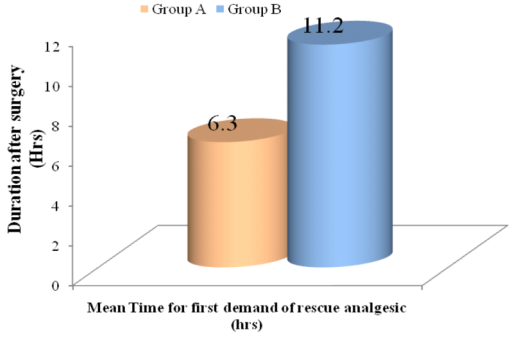

Figure 3: Comparison of Group A, B with respect to mean time for demand of rescue analgesia

Table 10: Total Analgesic Requirement within 24 hrs after surgery

Total consumption of ketorolac	Number and % of patients Required total dose of analgesic within 24 hrs after surgery				Pvalue
	Group A		Group B		
	No	%	No	%	
30mg	2	6.7	16	53.3	
60mg	8	26.7	14	46.7	
90mg	19	63.3	0	0	
120mg	1	3.3	0	0	
Mean ± SD	79.00±20.06 mg		44.00±15.22 mg		<0.001**

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