Spinal Anaesthesia with Hyperbaric Solutions of Ropivacaine, Levobupivacaine or Bupivacaine in Major Orthopedic Surgery

Büyük Ortopedik Cerrahi Girişimlerde Hiperbarik Ropivakain, Levobupivakain ya da Bupivakain Çözeltileri ile Uygulanan Spinal Anestezi

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ABSTRACT Objective: The aim of the present study was to compare the reliability, suitability and the side effects of the spinal blocks produced by hyperbaric solutions of levobupivacaine, ropivacaine and bupivacaine in patients undergoing total hip or knee arthroplasty. **Material and Methods:** Ninety patients, aged 30-75 years with American Society of Anesthesiology (ASA) grade I-III, undergoing total hip and knee arthroplasty were included in the study and randomized into three groups. Spinal anesthesia was performed in all patients; among the study groups in Group HB 3 ml of 0.5% hyperbaric bupivacaine, in Group HR 3 ml of 0.5% hyperbaric ropivacaine and in Group HL 3 ml of 0.5% hyperbaric levobupivacaine were given intrathecally. The same surgeon performed all the operations. **Results:** The mean duration of complete motor block was longest in Group HB($p=0.047$). Onset of sensory block at dermatome level T10 was earliest in Group HL($p<0.002$). Regression time of sensory block to dermatome level T10 and L1 was longest in group HB and shortest in group HR ($p<0.05$). First analgesic requirement was earliest in Group HR. More patients in Group HB required treatment for hypotension. Nausea/vomiting were significantly higher in Group HB ($p<0.05$). Incidence of hypotension was lowest in Group HR ($p<0.001$). **Conclusion:** In 15 mg doses, hyperbaric levobupivacaine showed similar potency and block characteristics to hyperbaric bupivacaine, and the duration of motor and sensory block was the shortest with hyperbaric ropivacaine. Levobupivacaine and ropivacaine had fewer side effects.

Key Words: Levobupivacaine; ropivacaine; orthopedics

ÖZET Amaç: Bu çalışma, total kalça ya da diz artroplastisi geçiren hastalarda hiperbarik ropivakain, levobupivakain veya bupivakain ile yapılan spinal anestezinin güvenilirliğini, uygunluğunu ve yan etkilerini karşılaştırmak amacıyla yapıldı. **Gereç ve Yöntemler:** Yaşları 30-75 arasında değişen, Amerikan Anesteziyologlar Derneği (ASA) sınıflamasına göre sınıf I - III arasında olan ve total kalça ya da diz artroplastisi geçirecek 90 hasta çalışmaya alınarak randomize şekilde üç gruba ayrıldılar. Her üç gruba da spinal anestezi uygulandı; çalışmada yer alan gruplardan Grup HB'ye 3 ml %0.5 hiperbarik bupivakain, Grup HR'ye 3 ml %0.5 hiperbarik ropivakain ve Grup HL'ye 3 ml %0.5 hiperbarik levobupivakain intratekal olarak verildi. **Bulgular:** Motor blok süresi en uzun olan Grup HB idi ($p = 0.047$). Dermatom T10 düzeyinde en erken duyusal blok ortaya çıkışı Grup HL'de gözlendi ($p < 0.002$). Duyusal bloğun dermatom T10 ve L1 düzeyine gerileme süresinin grup HB'de en uzun, grup HR'de ise en kısa olduğu görüldü ($p < 0.05$). İlk olarak analjezik gereksinimi ortaya çıkan grup ise HR grubu oldu. Grup HB'de daha fazla sayıda hastanın hipotansiyon açısından tedavi edilmesi gerekti. Bulantı ve kusma da Grup HB'de diğer gruplarda olduğundan anlamlı derecede daha fazla idi ($p < 0.05$). Hipotansiyon insidansının en düşük olduğu grup Grup HR idi ($p < 0.001$). **Sonuç:** Eşit dozlarda kullanıldıklarında hiperbarik levobupivakain ile hiperbarik bupivakainin etkinliklerinin ve blok oluşturma özelliklerinin benzer olduğu gözlendi. Diğer yandan, en kısa süreli motor ve duyusal blok hiperbarik ropivakain ile sağlandı. Levobupivakain ve ropivakainin daha az oranda yan etkiye yol açtıkları da saptandı.

Anahtar Kelimeler: Levobupivakain; ropivakain; ortopedi

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Two long-acting local anesthetics, ropivacaine and levobupivacaine, have been introduced to clinical use. Levobupivacaine and ropivacaine are the two local anesthetics that seem to be rational alternatives to bupivacaine due to their significantly low cardiovascular[1,2] and central nervous system[3,4] toxicities. Comparative clinical studies have been conducted with these two agents for non-obstetric[5,6] and obstetric epidural anesthesia,[7] brachial plexus block,[8] infiltration analgesia[9] and for spinal anesthesia.[10]

In the previous studies, hyperbaric solutions of ropivacaine and levobupivacaine were used in small doses for unilateral spinal blocks for outpatient knee arthroscopy[11] and for inguinal hernia repair.[6]

Hyperbaric solution of ropivacaine is also used for unilateral block in higher doses for lower extremity surgery[12] and isobaric ropivacaine is used in major orthopedic surgery in high doses for bilateral blocks.[13] The effects of hyperbaric forms of the three local anesthetic agents bupivacaine, ropivacaine and levobupivacaine in high-dose unilateral blocks in major orthopedic surgery have not been studied previously.

In this prospective, randomized clinical study, clinical reliability and suitability of the sensory and motor blocks produced by intrathecal application of hyperbaric levobupivacaine, ropivacaine and bupivacaine were compared in patients undergoing total hip or knee arthroplasty.

MATERIAL AND METHODS

Ethical committee approval (16.03.07, 07005) of a Medical School and the written informed consents of the patients were obtained for this prospective study. Patients were randomly allocated into three groups by closed envelopes. Ninety adult patients undergoing elective primary unilateral total knee or hip arthroplasty, ASA classification I-III, age 30 -75 years, height >150 cm and weight 50 -100 kg were included in this study. Patients with contraindication to spinal anesthesia, allergy to amide local anesthetics and bleeding disorders were not included.

All patients were premedicated with intramuscular injection of 0.5 mg atropine sulphate and 0.05mg /kg midazolam 45 minutes before the operation. As it is routine at this institution, all spinal blocks were performed outside the operating room (OR) in a properly designed block room. Following arrival in the block room, intravenous route was established with a 20-gauge IV cannula at the dorsum of left hand and 100 mg ranitidine and 10 mg metoclopromide were administered intravenously. Continuous monitoring of electrocardiogram (ECG), noninvasive arterial pressure and pulse oxymetry were started. After infusing 500 ml of lactated Ringer's solution over a period of 30 minutes, patients were placed in lateral position on the effected side. Dural puncture was performed with the midline approach at the L3-4 or L4-5 interspace using a 25-gauge Whitacre spinal needle. Correct needle positioning was confirmed with free flow of cerebrospinal fluid, and 3 ml of study drug was injected intrathecally. The same surgeon performed all the operations.

Using computer generated sequence of numbers and a sealed envelope technique, patients were randomized into three groups: the first group received 15 mg of 0.5% hyperbaric bupivacaine (group HB, n=30), the second group received 15 mg of 0.5% hyperbaric ropivacaine (group HR, n=30) and the third group received 15 mg of 0.5% hyperbaric levobupivacaine (group HL, n=30).

The hyperbaric anesthetic solutions were aseptically prepared immediately before injection by an anesthesiologist who was not involved in further patient care.

Each of the patients in the study received 3 ml of one of the three solutions: bupivacaine (Marcaine: bupivacaine hydrochloride, AstraZeneca, Sweden) 5 mg ml^{-1}, levobupivacaine (Chirocaine: levobupivacaine hydrochloride, Abbot Laboratories, UK) 5 mg ml^{-1}, or ropivacaine (Naropin: ropivacaine hydrochloride, AstraZeneca, Sweden) 5 mg ml^{-1}, each with 30 mg ml^{-1} glucose. Density of the local anesthetic solutions were (g ml^{-1}) 1.00874, 1.00945, 1.00876 for bupivacaine, levobupivacaine and ropivacaine, respectively.[14]

After free flow of cerebrospinal fluid was observed, the opening of the spinal needle was turned

toward the dependent side and the prepared dose of local anesthetic solution was injected slowly (injection speed: 0.1mL/sec) without further aspiration maneuvers. The lateral decubitus position was maintained for a 15-min period; afterwards, patients were turned supine, transferred to the operating room and the operation was initiated.

The development of the block was evaluated and recorded using pin prick tests for sensory block, and modified Bromage scale (0=no motor block, 1=inability to raise extended legs, 2=inability to flex knees, and 3=inability to flex ankle joints) was used to determine the degree of motor block at 1 st, 3 rd, 5 th, 10 th, 15 th and 20th minutes. Arterial blood pressure and heart rate were recorded at 1 st, 3 rd, 5 th, 10 th, 15 th and 20th minutes and at every 20 minute thereafter until complete regression of the block. The onset and the duration of sensory block at dermatome level T10, maximum upper and lower spread of sensory block, and the onset (modified Bromage scale 3), intensity and duration of motor block were recorded. After the sensory block was achieved at dermatome level T10, surgery was allowed to start.

Hypotension (30% or more decrease in mean arterial blood pressure (MAP) from the baseline value) was treated with boluses of IV ephedrine (5 mg) and crystalloid infusion until the normotensive state was achieved. If hypotension was not responsive to two consequent boluses of ephedrine and crystalloid infusion a volume expander (Hydroxyethyl starch (HES 130/0.4) in isotonic sodium chloride solution (Voluven, Germany, 500 mL) was infused. Bradycardia (30% or more decrease in heart rate (HR) from the baseline value) was treated with 0.5 mg IV atropine. High sensory block level, sensory block level below dermatome T10, agitation, nausea and vomiting were the other undesired effects that were observed during surgery.

The quality of the anesthesia (judged by the anesthetist), the quality of muscle relaxation (opinion of the surgeon) and the degree of intraoperative comfort (judged by the patient) were recorded as 1: unsatisfactory, 2: satisfactory and 3: excellent.

The time to regression of sensory block in dermatomes T10 and L1 (by using pin prick test) was recorded as well as the hemodynamic parameters and bilateral levels of both sensory and motor blocks at 0, 20, 40, 60 and 120 minutes after the completion of the surgery.

The patients were evaluated for the presence of nausea, vomiting, fever, headache and backache during the first 24 hours following the surgery. Intraoperative blood loss and the time of first request for analgesic medication were also recorded.

STATISTICAL ANALYSIS

The calculation of the required sample size was based on mean and standard deviation of complete regression of spinal anesthesia with bupivacaine, ropivacaine and levobupivacaine.[10,15] Thirty patients per group were required to detect a 20- min difference in time for complete regression of spinal anaesthesia and expected effect size to standard deviation ratio of 0.9, accepting a two-tailed alpha error of 5% and a beta error of 20%.

SPSS For Windows 11,5 Program was used for statistical analysis.

Mean ± standard deviation or median [25%-75% percentiles] were given for numerical data as appropriate. Nominal data were presented by frequencies. Data distribution was evaluated for normality by Kolmogorov Smirnov test. Comparisons of numeric data between the groups were performed by one way ANOVA followed by Tukey HSD test, or Kruskal Wallis test followed by Dunn test. Nominal data among study groups were compared using Chi-square analysis. For the evaluation of hemodynamic parameters during the operation, comparisons within the groups were made by analysis of variance in repeated measurements with the Tukey HSD test for between groups and Bonferroni test for within groups post hoc comparisons. A p value less than 0.05 was considered as statistically significant.

RESULTS

There was no statistically significant difference between the study groups for the demographic parameters, age, weight, height, sex, ASA classification, accompanying disease or use of medication (p>0,05)

TABLE 1: Demographic data, operation type (knee/hip), side of the operation (right/left) and duration of the operation. No significant difference.

	Group HB (n=30)	Group HR (n= 30)	Group HL (n=30)	P
Age (year)	65,5±11,5	68,5±7,7	67,3±8,3	0,440
Weight (kg)	76,4±16,1	76,9±19,3	75,8±10,5	0,964
Height (cm)	160,9±8,1	159,0±18,8	162,2±5,1	0,600
Female/Male	17/13	19/11	18/12	0.870
ASA (I-II/III)	26 / 4	27 / 3	23 / 7	0.343
Knee/Hip	16/14	18/12	12/18	0.286
Side (right/left)	12/18	14/16	14/16	0.835
Duration of the Operation (min)	107,2±54,3	106,6±48,3	86,3±34,5	0,146

Group HB: received 15 mg of hyperbaric bupivacaine, Group HR: received 15 mg of hyperbaric ropivacaine, Group HL: received 15 mg of hyperbaric levobupivacaine.
Values are represented as mean ±SD or as number.

(Table 1). There were no statistically significant differences between the groups with regard to operation type (knee/hip), side of the operation (right/left) or duration of the surgery (Table 1).

The time to sensory block reached T10 and Bromage scale 3 was significantly longer in Group HR ($p<0.05$) (Table 2).

Time for the sensory block to regress to T10 and L1 was the longest in Group HB and the shortest in Group HR (Table 2).

The duration of motor block was the longest in Group HB, the shortest in Group HR and the difference was found to be statistically significant ($p<0.05$) (Table 2).

Time to first postoperative analgesic requirement was similar between the study groups ($p>0.05$) (Table 2). Maximal upper sensory level of the block detected by pin prick test on the operated side is presented in Table 3.

In each of the three groups, there was a significant difference in height of sensory level between the operated and nonoperated sides; however, no differences were found between the three groups (Figure 1).

The number of the patients with hypotension who required intravascular volume expanders was highest in Group HB and this result was statistically significant ($p< 0.001$) (Figure 2). Bradycardia necessitating treatment was not observed in any of the patients (Figure 3).

The number of the patients with nausea or vomiting was highest in Group HB, and this was found to be statistically significant ($p< 0.001$).

There were no serious postoperative complications or postdural puncture headache in the patients. Efficiency and quality of the anesthesia, ease of the manipulation and patient satisfaction were similar between the groups.

DISCUSSION

In this study, clinical and anesthetic features and side effects of hyperbaric solutions of levobupiva-

TABLE 2: Characteristics of motor and sensory block with the three medications. range for maximal upper spread

	Group HB (n=30)	Group HR (n=30)	Group HL (n=30)	P
Sensory onset time(T10) (min)	4,5±2,1	6,2±2,4*	5,6±4,4	0.009
Onset of motor block (min)	5,1±2,5	5,8±2,7*	4,8±2,6	0.029
Time to T10 regression (min)	138,6±28,6	122,6±10,9**	135,4±16,6	0,007
Time to L1 regression (min)	172,4±33,5	143,5±14,3**	151,3±25,5	<0,001
Duration of motor block (min)	166,3±40,8	128,6±37,6**	146,5±33,2	0,047
First request for analgesic (min)	228,7±61,2	207,5±65,3	211,6±54,6	0,369

Group HB: received 15 mg of hyperbaric bupivacaine, Group HR: received 15 mg of hyperbaric ropivacaine, Group HL: received 15 mg of hyperbaric levobupivacaine.
*HR longer compared to HB and HL
**HR shorter compared to HB and HL
Values are represented as mean ±SD or as median[25%-75% percentiles].

TABLE 3: Maximal upper sensory level of the block.

	Group HB	Group HR	Group HL
Th_3			
Th_4	⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡	⊡⊡	●●●
Th_5	⊡⊡⊡⊡	⊡	●●●●●●
Th_6		⊡⊡⊡	●●●●●●●●●
Th_7	⊡⊡⊡⊡⊡	⊡⊡⊡⊡⊡	●●●
Th_8		⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡⊡	●●●●●
Th_9	⊡⊡⊡⊡⊡	⊡⊡	
Th_{10}	⊡⊡	⊡⊡	●●●●

Each symbol (●,□,⊡) represents one patient.
Group HB: received 15 mg of hyperbaric bupivacaine, Group HR: received 15 mg of hyperbaric ropivacaine, Group HL: received 15 mg of hyperbaric levobupivacaine.
Range for maximal upper spread, Th= Thoracic

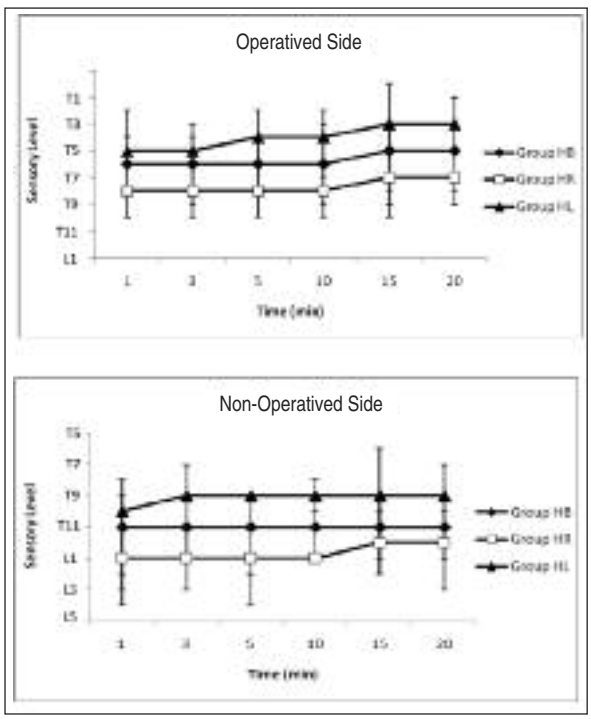

FIGURE 1: Median (range) sensory block recorded on both operated and non-operated sides during the first 20 min after spinal injection of 15mg of hyperbaric bupivacaine (Group HB n=30), 15mg of hyperbaric ropivacaine (Group HB n=30) or 15mg of hyperbaric levobupivacaine (Group HL n=30).

caine, ropivacaine and bupivacaine for spinal anesthesia were compared in patients undergoing total hip or knee arthroplasty.

Ropivacaine and levobupivacaine have been increasingly used for spinal anesthesia, but little information is available regarding their use for major orthopedic surgery.[13] McDonald et al. have reported that when the dose/effect relationship of hyperbaric ropivacaine and bupivacaine were compared, ropivacaine exhibited 50% lower potency than bupivacaine.[16] However, Casati et al. have recently reported that 8 mg of hyperbaric levobupivacaine or 12 mg of hyperbaric ropivacaine were acceptable alternatives to 8 mg of hyperbaric bupivacaine when spinal anesthesia was limited to the operation side for inguinal hernia repair, but the use of a 1.5 to 1 equipotency ratio between ropivacaine and levobupivacaine resulted in a shorter duration of spinal anesthesia with ropivacaine.[6] Similar results have also been reported by Danelli et al. during spinal anesthesia for Caesarean delivery.[17] In a recent study Luck and colleagues found that hyperbaric ropivacaine produced a spinal block with sensory block onset characteristics similar to equivalent doses of hyperbaric bupivacaine or levobupivacaine, however the motor block was less intense.[14]

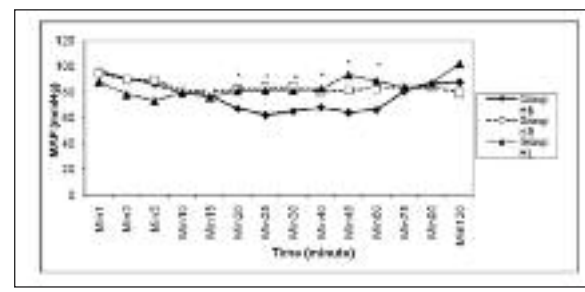

FIGURE 2: Bars represent mean arterial pressures (MAP) after spinal anesthesia for each group. The extended bars represent SD.
*Indicates a statistically significant difference between groups (p<0,05). p>0,05 for within groups and group-time interaction

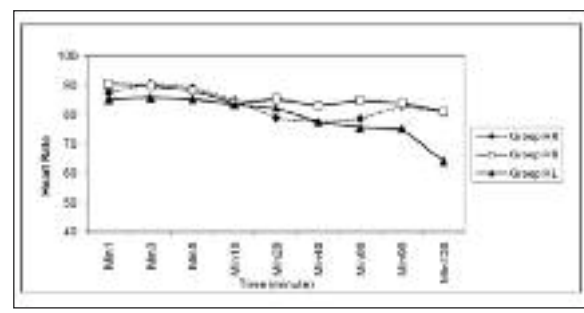

FIGURE 3: Heart rate (HR) in the three groups were similar during and after the surgery (p>0.05 for between groups, within groups and group-time interaction).

In this study, relatively higher doses of local anesthetics were chosen when compared to minor surgical interventions (e.g.; arthroscopies). Since the duration of the surgery in total joint replacement is longer than arthroscopic knee surgery or inguinal hernia repair, more muscle relaxation is desired. Glaser et al. compared racemic solutions of levobupivacaine (17.5 mg) with bupivacaine (17.5 mg) in eighty hip replacement patients.[18] They found that the number of the patients experiencing adverse hemodynamic events was considerably low in both groups (one patient in levobupivacaine group and two patients in the bupivacaine group), and concluded that the efficacy of intrathecal levobupivacaine was equal to, but less toxic than racemic bupivacaine.

So far, only one clinical trial by Fattorini et al. compared the effects of isobaric levobupivacaine (15 mg) and bupivacaine (15 mg) in 60 patients undergoing hip and knee replacement surgery.[19] Characteristics of motor and sensory block were found similar although severe hypotension was noted in two elderly patients (n=2/30) in the bupivacaine group.[19] Up to the authors' knowledge, this study is the only comparative trial between the three local anesthetics, levobupivacaine (15 mg), ropivacaine (15 mg) and bupivacaine (15 mg), in their hyperbaric forms and for major orthopedic surgery.

Although relatively high levels of sensory block were obtained in all groups, the incidence of hypotension (30% decrease compared to basal measurement) was significant only in bupivacaine group (n=14/30) (p= 0.001). Side effect profiles of levobupivacaine, ropivacaine and bupivacaine were evaluated in a single study design previously. Whiteside et al. compared the side effects of hyperbaric bupivacaine (15 mg) and ropivacaine (15 mg) in a non- homogenous patient population, and reported that hypotension requiring treatment was observed in 70% (n=14) in bupivacaine group opposed to in 15% (n=3) in ropivacaine group.[12] In this study, the number of the patients who experienced hypotension requiring volume expanders in groups HB, HR and HL were 14, 3 and 4, respectively. The most remarkable result of this study was that the prevalence of hypotension leading to hemodynamic instability and induced nausea and vomiting was higher with bupivacaine.

Whiteside et al. previously compared the characteristics of 15 mg of ropivacaine and bupivacaine in their hyperbaric forms.[12] The main outcome of the study was that hyperbaric (50 mg ml^{-1}) ropivacaine provided reliable spinal anesthesia for shorter duration and less hypotension than bupivacaine. Eventhough the results of the current study seems to be similar; the major difference is the presence and comparison with the levobupivacaine group. Questions may rise for the dosage used in this study as different doses of these local anesthetics were used in recent studies. The main reasons were the need for more muscle relaxation, and the lack of previous studies with the hyperbaric forms of these local anesthetics in major orthopedic surgery. The recent study involving the patients undergoing elective Caesarean section delivery reveals that bupivacaine is more potent than levobupivacaine and ropivacaine.[17] On the other hand, the authors believe that the anesthesia requirements and the desired motor block characteristics of the major orthopedic surgery is truly diverse compared to Caesarean section.

That is why the results of this recent study can not be interpreted for different types of surgery. However, further studies are needed to evaluate the clinical efficacy of equipotent doses of these local anesthetics when used for spinal anesthesia in patients undergoing major orthopedic surgery.

In this study adequate anesthesia was obtained with all of the local anesthetics. However when the regression times of block to T10 and L1 were compared, the longest regression time was observed with bupivacaine followed by levobupivacaine and ropivacaine ($p<0.01$). The time to the first analgesic requirement was shortest with ropivacaine. However this difference was not statistically significant. When compared to bupivacaine, ropivacaine can provide better cardiovascular stability, but its potency is low. Levobupivacaine, on the other hand, has similar potency to bupivacaine and can provide good cardiovascular stability comparable to ropivacaine.

CONCLUSION

In 15 mg doses, hyperbaric levobupivacaine showed similar potency and block characteristics to hyperbaric bupivacaine while the duration of motor and sensory block in hyperbaric ropivacaine was the shortest. Levobupivacaine and ropivacaine had fewer side effects.

With these findings it can be concluded that levobupivacaine at the volume and concentration as used in the presented study can be the preferred agent in major orthopedic surgical cases.

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