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EFFECTIVENESS OF FIBRIN SEALANT AFTER CEMENTLESS TOTAL HIP REPLACEMENT: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

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Fibrinogen-based sealants have been used to improve hemostasis after total hip replacement (THR) with conflicting results. We therefore conducted a double-blind randomized controlled trial to determine whether the commercially available fibrin sealant Quixil is effective in reducing the volume of red blood cell transfusions, postoperative blood loss and postoperative hemoglobin drop. Patients with coxarthrosis scheduled for primary cementless THR, were enrolled in a single hospital setting and randomized to either a fibrin sealant group (n=35) or a negative control group (n=35). The surgeon was blind to group allocation until the moment of fibrin application, while the cardiologist determining the need for transfusions remained blind throughout the intervention. In the fibrin sealant group, less blood was lost in the first 48 hours (median, 125 *vs* 200 ml), fewer patients required allogeneic blood transfusion (1 *vs* 6 in the control group), and fewer total units of allogeneic blood were transfused (2 *vs* 12). These differences, however, were not significant partly due to confounding from the use of autologous transfusion of predeposited blood (according to a more liberal regime) and intraoperative autologous blood reinfusion in some patients of both groups. Excluding these last individuals from analysis, no remaining patient of the fibrin sealant group had an allogeneic blood transfusion that, instead, was carried out on 5 patients (23.8%) of the control group (p=0.048). Overall postoperative hemoglobin drop from baseline was significantly less in the fibrin-treated group on day 7 (mean, 3.5 *vs* 4.5 g/dl; p=0.02). No adverse events were associated with fibrin treatment. These results strengthen the evidence in support of the safety and efficacy of the use of fibrin sealant in improving hemostasis after THR. Clinical trial registration: EudraCT 2008-002024-28.

Joint replacement can expose patients to massive perioperative bleeding. When standard procedures are used, perioperative blood loss in primary total hip replacement (THR) can exceed 1 liter (1-3). This hematic loss results in a high rate of blood transfusion after THR (4-6). Blood transfusion can be used as a systemic method to solve blood loss but has the disadvantages of shortage of supply (7), high costs (8) and health risks (9, 10) of allogeneic blood units. In particular, allogeneic blood transfusion may result in the transmission of infectious diseases (11-13) or cause various severe immunomediated adverse reactions (14, 15). As a result, several blood conservation techniques, such as hemodilution (16), intra- and post-operative blood recovery (17), preoperative autologous blood donation (18), hypotensive anesthesia (19) and intravenous administration of tranexamic acid (20-22), have been developed to reduce the need for blood

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transfusion. Nevertheless, these alternative techniques are not risk free (23). Ideally, the best choice is to reduce hematic loss by improving intra- and post-operative hemostasis.

In the last decade, the topical use of fibrinogen-based sealants has become an attractive surgical practice for reducing blood loss in total arthroplasty of the knee (24, 25) and hip (26-29). Studies regarding THR investigated autologous fibrin preparations (28, 29) or the commercially available (off-the-shelf) product Quixil (Omrix Biopharmaceuticals, Tel Hashomer, Israel) (26, 27), with conflicting results: two randomized controlled trials (RCTs) reported that fibrin sealant significantly reduced postoperative blood loss without effecting the need for transfusion (27, 29), while another RCT (28) found no effect on either parameter and an early retrospective study reported a reduced need for transfusion only (26). Thus, there remains a doubt as to the real efficacy of fibrin sealants in THR. For this reason, we conducted a double-blind RCT to evaluate the effectiveness of Quixil fibrin sealant as a topical hemostatic agent in primary cementless THR. The aim of the study was to evaluate the ability of fibrin sealant to reduce the volume of red blood cell (RBC) transfusions, the postoperative hemoglobin drop and the postoperative blood loss compared to a control group.

MATERIALS AND METHODS

This double-blind RCT was conducted in a single hospital setting. The study protocol was approved by the competent ethics review committee (Comitato Etico Indipendente ASL Milano 2, Melegnano). The trial was registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) with the registration number 2008-002024-28. Throughout the study, a patient privacy policy was upheld.

Participants

In the study patients were enrolled aged 35-80 years with coxarthrosis who were scheduled for primary cementless THR. Exclusion criteria were: serious hip deformity, previous surgical intervention of any kind on the hip to be replaced, autoimmune or blood diseases, previous anaphylaxis to hemoderivatives, previous exposition to fibrin sealant, preoperative treatment with erythropoietin or hemodilution, anticoagulation or antiaggregant therapy of any nature that had not been suspended at least 7 days before surgery, pregnant or nursing women. Eligible patients were given detailed information about the study and those who agreed gave written informed consent to participate.

To determine the necessary sample size, a power analysis was made considering the effects of fibrin sealant on the volume of blood transfused. Considering 270 ml as the mean volume of one RBC unit and an average of 0.83 RBC units transfused (26) we established a mean RBC volume of 225 ml transfused after THR. To detect a significant 50% difference in RBC volume transfused between the groups (equal to 112.5 ml) with a standard deviation of 135 ml (one-half RBC unit) and accepting $\alpha = 0.05$ and power = 0.90, it was necessary to enroll 31 patients per group. With a dropout rate of 10%, this number was increased to 35 patients per group. Therefore, 70 patients were consecutively enrolled between September 2008 and June 2009.

According to standard hospital policy, the patients were evaluated for the possibility of depositing 1-2 units of blood preoperatively, according to established criteria (30, 31). All those who met these criteria deposited autologous blood four weeks before the operation.

Study product

The fibrin tissue adhesive used in the present study was Quixil® Human Surgical Sealant Kit (Omrix Biopharmaceuticals). It consists of a packet containing two components in two separate 5-ml vials: vial I contains a concentrate of human fibrinogen (40-60 mg/ml) with tranexamic acid (85-105 mg/ml) added as stabilizer; vial II contains human thrombin (800-1200 IU/ml) in a calcium chloride solution (5.6-6.2 mg/ml). The two components were combined by mixing just before use.

Randomization and masking

Patients were randomized at a 1:1 ratio to the experimental (fibrin sealant) group or to a control group. The randomization was determined according to patient number, which had been assigned with a computer-generated blocked randomization list.

The operative procedures were performed in blind by a team of 5 surgeons from the same surgical department. Only at the end of the operation, at tissue closure, was the first surgeon provided with information on each patient's group allocation. This procedure was adopted to eliminate potential bias related to the surgeon during the operation. Double-blinding was achieved by masking patients' group allocation from the single cardiologist assigned the responsibility of deciding the need for allogeneic or autologous blood transfusion in the postoperative period.

Intervention

Enoxaparin, for thromboembolic prophylaxis,

was started 12 hours before surgery and continued for 35 days. The anesthesiologic procedure consisted in combined spinal-epidural anesthesia with general anesthesia. Tranexamic acid (10 mg/kg) was administered intravenously in the immediate preoperative period (approximately 10 min before incision) to reduce bleeding which is our standard practice. Mean arterial pressure was maintained at 60-65 mmHg.

THR was performed through a trans-gluteal lateral approach with the patient supine. Hemostasis was carried out using unipolar electrocoagulation. Intraoperative blood recovery was performed according to our anesthesiological procedure. After cementless implantation of the acetabular and femoral components and just before closure, the treatment allocation was given to the surgeon. For patients assigned to the treatment group, the adhesive fibrin solution (10 ml) was applied topically through a double-syringe spraying device connected to pressurized air (2 bar). The fibrin sealant was sprayed over the dried operative field from an approximate distance of 10 cm, starting medially from the inner part of the joint space and proceeding laterally, over the cut bone surface of the femur and over soft tissues in order to cover with a fibrin glue film as much tissue surface as possible, all over the operative field. For patients assigned to the control group, physiological saline was used to wash the operative field.

One non-vacuum drain, connected to a hemorecovery bottle, was inserted into the hip joint space. The tissues were then closed with layered sutures and the skin was closed with intradermic sutures. The hemorecovery bottle was hung on the patient's bed at floor level, without connection to a vacuum device. At the end of surgery, a continuous peridural infusion of 0.125% levobupivacaine (7 ml/h) was started and continued for 36-48 hours. The drain was removed 48 hours after surgery. Patients received indomethacin (50 mg/day) as heterotopic ossification prophylaxis, starting the second day after surgery and continuing for 20 days. In order to prevent thromboembolic events, bilateral thigh-foot graduated elastic compression socks were used postoperatively for two months. Active mobilization and rehabilitation began on the second day.

Transfusion criteria

The need for transfusions was decided according to the practice guidelines of the American Society of Anesthesiologists (32) and based on hemoglobin levels, which were measured preoperatively and postoperatively on the first, second, third and seventh days and at the 1- and 2-month follow-up visits. The decision to proceed with transfusion varied according to whether or not patients had deposited autologous blood. For those without blood deposits, a hemoglobin level of 8.5 g/dl was taken as transfusion threshold (31, 32). For those with autologous blood deposits, a more liberal regimen was employed, namely a hemoglobin level of 10 g/dl or less (31). Nonetheless, the final decision to proceed with transfusion also considered other clinical parameters, since the inadequacy of a single transfusional trigger is well recognized (31, 32).

Data collection

To assess the homogeneity of the groups, we registered the following independent variables: sex, age, body mass index, presurgical deposition of autologous blood, baseline hemoglobin levels, surgical time, surgical wound length, subcutaneous fat thickness, intraoperative blood loss and intraoperative blood recovery (autotransfusion). Intraoperative blood loss was the volume recovered by the intraoperative blood recovery system, excluding that of the irrigation solution used. Since blood lost on the operative field or collected with gauze could not be assessed, we attempted to minimize these losses by applying a collection bag connected to the aspiration circuit on the operating field. Postoperative blood loss was assessed in the first 48 hours after surgery, from the total volume collected in the hemorecovery bottle. The number and type (allogeneic or autologous) of transfused RBC units during hospitalization were recorded.

Drug safety was evaluated during hospitalization and at the 1-month and 2-month follow-up visits. Blood parameters (erythrocyte sedimentation rate, C-reactive protein, complete blood count) were assessed and hospitalization time and rehabilitation time were recorded. All adverse events and postoperative complications (including delayed wound healing, wound dehiscence and secretion, hematomas, sign of infection, deep venous thrombosis, pulmonary embolism, urinary tract infections) were recorded.

Statistical methods

Differences between groups were tested for significance with an unpaired *t*-test (normal distributions) or with the Mann-Whitney test (skewed distributions), while associations among variables were tested with the *chi*-square test or Fisher's exact test.

Postoperative changes in hemoglobin and hematocrit were assessed over time by progressively excluding any patient who had a blood transfusion; this was done to avoid confounding by the subsequent increase in hemoglobin in these patients. To correct for individual variations in baseline values of these parameters, we calculated the difference between the preoperative value and the postoperative value at each follow-up time ($\Delta Hb = Hb_{preop} - Hb_{postop}$; $\Delta Ht = Ht_{preop} - Ht_{postop}$).

Since clinical variables were repeatedly measured

over time, a multivariate analysis of variance (MANOVA) for repeated measures was carried out.

Statistical analysis was carried out using SPSS for Windows, release 10.0 (SPSS Inc, Chicago, USA). All reported p values are two-tailed. A p value <0.05 was considered to indicate statistical significance.

RESULTS

The 70 patients who were enrolled in the trial all received the treatment as allocated at randomization and all were followed through to the end of the study (Fig. 1). Baseline clinical characteristics and surgical parameters were similar in the two groups (Table I). In particular, 11 (31.4%) patients in the fibrin sealant group and 9 (25.7%) patients in the control group deposited 1-2 RBC units preoperatively ($p > 0.05$, *chi*-square test). Preoperative hemoglobin levels were slightly higher in the fibrin sealant group, but this difference was not significant despite the narrow data dispersion ($p > 0.05$, unpaired t-test). Intraoperative blood loss was also similar between groups and an identical number of patients in each group had intraoperative autologous blood reinfusion.

In the first 48 postoperative hours, blood loss from drainage was lower in the fibrin sealant group than in the placebo group (median, 125 *vs* 200 ml), but this difference was not significant due to the wide and overlapping range of values. No patient received both autologous and allogeneic blood. Overall, 8 of the 11 patients with autologous blood deposits in the experimental group and 7 of the 9 such patients in the control group underwent autologous transfusion and received exactly the number of units they had deposited. Allogeneic transfusion was carried out on 1 patient (2.8%) in the experimental group and 6 (17.1%) in the control group ($p = 0.1$, Fisher's exact test). Each patient received 2 allogeneic RBC units. Therefore, the total number of allogeneic RBC units transfused within the treatment and control groups was, respectively, 2 and 12.

Mean hemoglobin levels measured on postoperative days 1, 2, 3 and 7 were similar between groups when patients who received transfusions were progressively eliminated from analysis. To correct for individual variations in baseline values, changes in hemoglobin (ΔHb) and hematocrit (ΔHt) were calculated during the postoperative period: a significant difference between the two groups was found in ΔHb on postoperative day 7 ($p=0.040$, unpaired t-test) (Table II). For the other time points, the differences between groups were not significant.

A multivariate analysis performed for hemoglobin showed a general effect of intraoperative autologous blood recovery and reinfusion, with significantly higher mean values in patients who had their blood intraoperatively recovered, processed and reinfused than in those who did not ($p=0.03$, MANOVA). Therefore, to avoid confusion due to intraoperative autologous blood recovery and reinfusion, we did a post-hoc analysis limited to the 21 patients in each group who did not have this procedure. These patient subgroups were comparable for baseline and surgical parameters (data not shown). Allogeneic blood transfusion was carried out on 5 patients (23.8%) of the control group ($p=0.04$, Fisher's exact test) but on none of the patients of the fibrin sealant group. Progressively excluding patients who had transfusions, we observed a significantly higher mean (±SD) hemoglobin value 7 days after surgery in the experimental group (10.1±1.2 g/dl; n=21) compared to the control group (9.2±0.7 g/dl; n=21), ($p=0.029$, unpaired t-test) (Fig. 2). Furthermore, the drop in hemoglobin (ΔHb) from baseline to postoperative day 7 was significantly lower for the fibrin sealant group (3.5±1.1 *vs* 4.5±1.1; $p=0.02$). Similar behavior was seen for hematocrit on day 7: Ht, 30.8±3.5 *vs* 28.5±2.1; ΔHt, 10.0±3.4 *vs* 12.9±2.9 ($p=0.02$).

Considering the whole study population, the experimental and control groups had similar postoperative courses, both registering a mean 10 days in hospital and 16 days in rehabilitation in a step-down unit. Two serious adverse events occurred in the late postoperative period: one woman in the control group died from peritonitis 5 months after operation, and one woman in the experimental group had pulmonary embolism following deep venous thrombosis 10 days after the suspension of enoxaparin (i.e. 45 days after surgery). No minor adverse events were recorded.

DISCUSSION

In this study, use of fibrin sealant after THR resulted in a lower median postoperative blood loss, fewer

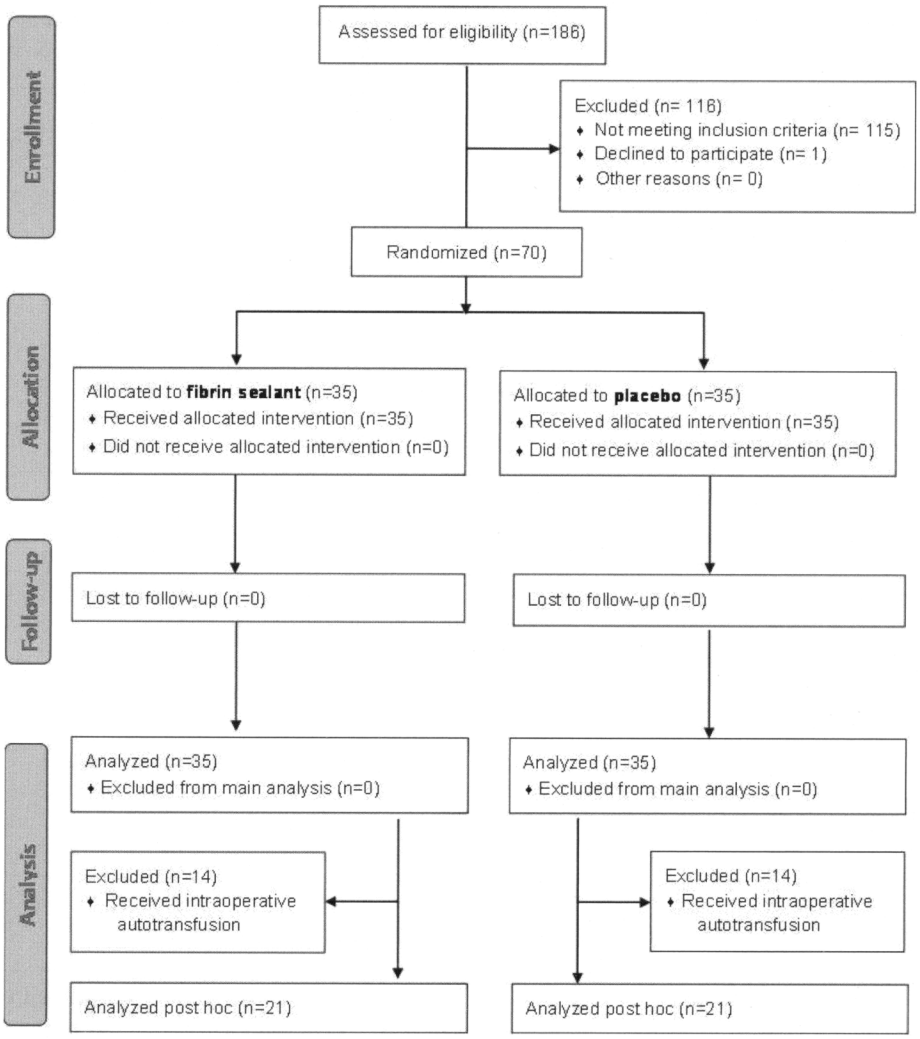

Fig. 1. *Study flowchart.*

patients requiring allogeneic blood transfusion, and fewer total units of allogeneic blood being transfused compared to control group (no fibrin sealant); however, these differences were not significant unless considering the post-hoc analysis in a subgroup of patients. Postoperative values of hemoglobin and hematocrit were similar between groups, yet the drop in hemoglobin from preop to day 7 was significantly less in the fibrin sealant group; this finding suggests that in fibrin-treated patients hemoglobin levels were starting to increase already by day 7.

Overall, relatively few patients in this study required allogeneic blood transfusion (1 patient (2.8%) in the experimental group and 6 (17.1%) in the control group) when compared to the previous RCT on Quixil fibrin sealant in THR: Wang et al. (27) reported that 29% of patients in the experimental group and 42% in the control group had transfusions. In both that study and the present one, these differences were not significant. The overall lower need for transfusion achieved in this study might be attributable to the preoperative administration of tranexamic acid to all patients and to the selective use of an intraoperative blood recovery and reinfusion,

Table I. *Clinical characteristics and surgical data for 70 patients who underwent total hip replacement.*

Parameter	Fibrin sealant (n = 35)	Control (n = 35)
Male, n (%)	16 (45.7)	13 (37.1)
Body mass index, mean (SD)	27.2 (4.9)	25.9 (4.6)
Age, years, mean (SD)	63.1 (11.8)	64.2 (11.8)
Preoperative hemoglobin, g/dl, mean (SD)	13.78 (1.16)	13.38 (1.38)
Patients depositing blood preoperatively, n (%)	11 (31.4)	9 (25.7)
Surgical time, min, mean (SD)	85 (15)	83 (15)
Surgical wound length, cm, mean (SD)	19.6 (2.5)	20.2 (2.0)
Subcutaneous fat thickness, cm, mean (SD)	5.3 (2.9)	5.3 (3.1)
Intraoperative blood loss, ml, median (range)	270 (50 – 720)	280 (0 – 760)
Intraoperative autologous blood reinfusion (28 patients)		
Patients, n	14	14
Volume, ml, median (range)	200 (150 – 650)	200 (150 – 500)

SD: standard deviation

Table II. *Postoperative drop in hemoglobin (Hb) and hematocrit (Ht) levels from baseline.*

Parameter	Treatment (n=35)	Control (n=35)	Unpaired t test, p
Hb change (ΔHb), g/dl, mean (SD); n[a]			
Day 1	2.8 (0.8); 35	2.9 (0.9); 34	> 0.05
Day 2	3.6 (1.1); 33	3.8 (0.9); 29	> 0.05
Day 3	4.0 (1.1); 31	4.2 (1.0); 25	> 0.05
Day 7	3.6 (1.1); 25	4.4 (1.2); 21	0.040
Ht change (ΔHt), g/dl, mean (SD); n[a]			
Day 1	8.4 (2.4); 35	8.6 (2.8); 34	> 0.05
Day 2	10.8 (3.4); 33	11.4 (2.7); 29	> 0.05
Day 3	12.0 (3.2); 31	12.7 (3.0); 25	> 0.05
Day 7	10.5 (3.4); 25	12.5 (3.6); 21	0.056

[a] *Patients who received transfusions were progressively eliminated from analysis*

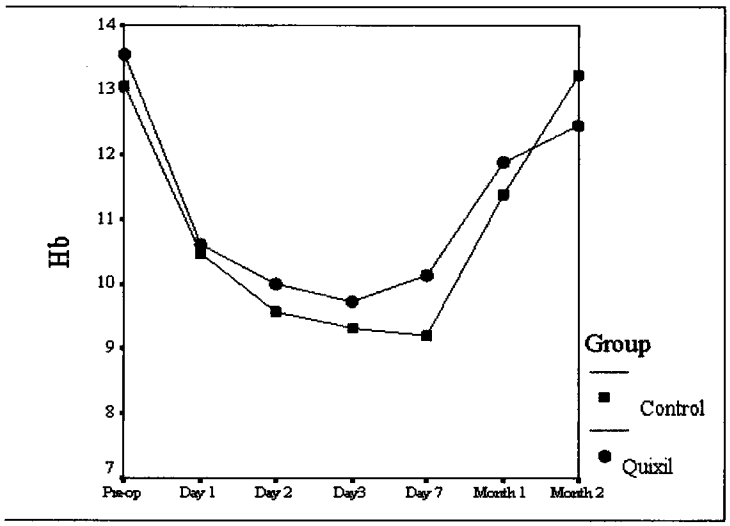

Fig. 2. *Mean hemoglobin values at baseline and throughout the postoperative period, for the 21 patients in each study group who did not have intraoperative autologous blood reinfusion. Patients who received postoperative transfusions were progressively excluded from analysis. Day 7, p=0.029, unpaired t-test.*

standard practices at our institute. Intraoperative blood recovery and reinfusion system is doubtless an autologous blood transfusion which influenced the postoperative hemoglobin drop and, thus, the requirement of further transfusions. Intraoperative blood recovery and reinfusion system was considered as bias for this study.

In fact, in a subgroup analysis limited to patients who did not intraoperatively receive reinfused autologous blood (shown by MANOVA analysis to influence postoperative hemoglobin values), the number of patients who received allogeneic transfusion within the control group resulted significantly higher than within the treatment group. Moreover, in this subgroup analysis the fibrin sealant had a significant positive effect on mean hemoglobin and hematocrit values and on changes in their values at day 7.

Two previous RCTs (27, 29) on the use of fibrin sealant in THR reported a significant reduction in postoperative blood loss that was not confirmed here. In one of these studies, this significant effect was observed only after adjusting for patient's body weight and baseline hemoglobin and for the surgeon who operated in the multicenter study (27). In the present single-center study, no adjustment was made to compensate for body weight or baseline hemoglobin. Another possible explanation for the lack of a significant difference in postoperative blood loss is our choice to use a single gravity drain rather than 2-3 aspiration drains, as in the other studies.

Our results suggest that the fibrin sealant exerts its effects later in the postoperative period, after the first 48 hours. This possibility is supported by our observation that significant benefits of fibrin treatment on hemoglobin and hematocrit were only observed on postoperative day 7.

Another limitation of this trial inherent in the original study design has been related to autologous blood predeposition. As per hospital practice, some patients preoperatively deposited autologous blood, which was liberally transfused in the postoperative period according to criteria different from those applied in the transfusion of allogeneic blood.

In this trial, as in previous studies (26, 27), intraoperative application of fibrin sealant was not associated with minor or severe adverse events.

Our results, even if with some limitation bias adjusted in the post hoc analysis, strengthen the evidence for the effectiveness and safety of the topical

use of human-derived fibrin sealant in improving hemostasis after primary cementless THR.

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