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Prevention of Anterior Scar Formation Following Discectomy with a MediShield Adhesion Barrier: Randomized Experimental Trial

Diskektomiyi Takip Eden Anterior Skar Oluşumunun MediShield Yapışıklık Bariyeri ile Önlenmesi: Randomize Deneysel Çalışma

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ABSTRACT

AIM: To investigate whether carboxymethylcellulose/polyethylene oxide (CMC/PEO) gel has a protective effect against epidural scar formation anterior to the dura following discectomy.

MATERIAL and METHODS: A barrier gel comprised of CMC and PEO (MediShield) was studied as a material to reduce anterior epidural scar formation in a rabbit laminotomy and discectomy model. After laminotomy and disc puncture, the surgical side was either treated with MediShield or used as a surgical control, as determined by random allocation. Two months after surgery, the animals were euthanized, and their lumbar spines were removed in an en bloc excision for pathological evaluation. Scar formation was evaluated as present or absent.

RESULTS: The MediShield group contained 12 rabbits, and the control group contained 7 rabbits. Epidural fibrosis was observed in two out of twelve specimens (17%) in the MediShield group and in three of seven (43%) cases in the control group (P=0.305, Fisher's Exact Test).

CONCLUSION: Though it was not statistically significant, we observed a difference between the MediShield and control group that favored the MediShield group. The application of the CMC/PEO gel might protect against epidural fibrosis after lumbar discectomy, but its efficacy needs to be investigated in larger experimental trials.

KEYWORDS: Adhesions, Discectomy, Epidural, Fibrosis, Laminotomy

ÖZ

AMAÇ: Karboksimetilsellüloz/polietilenoksid (CMC/PEO) jelinin diskektomiyi takiben duranın anteriorundaki epidural skar oluşumuna karşı koruyucu etkisinin olup olmadığının araştırılması.

YÖNTEM ve GEREÇLER: CMC ve PEO'dan oluşan bariyer jel (MediShield), tavşanlarda laminotomi ve diskektomi modelinde, anterior epidural skar oluşumunu azaltmak için bir alet olarak kullanıldı. Laminotomi ve diskin delinmesinden sonra cerrahi taraf, random bölüştürmelerine bağlı olarak, ya cerrahi kontrol grubu olarak kullanıldı ya da MediShield ile tedavi edildi. Cerrahiden iki ay sonra hayvanlar ötanize edildi ve lomber omurgaları patolojik değerlendirmeleri için en blok eksizyon halinde çıkartıldı. Skar formasyonu var veya yok olarak değerlendirildi.

BULGULAR: Kontrol grubunda 7 tavşan vardı ve MediShield grubunu 12 tavşan oluşturdu. Epidural fibrozis kontrol grubundaki yedi olgunun üçünde (%43) mevcut iken MediShield grubundaki on iki örneğin ikisinde (%17) bulundu (P=0,305, Fisher's Exact Test).

SONUÇ: İstatistiksel olarak anlamlı olmamasına rağmen, MediShield ile kontrol grubu arasında MediShield grubu lehine bir fark bulduk. CMC/PEO jeli uygulamasının lomber diskektomi sonrası epidural fibrozis gelişiminin önlenmesinde pozitif bir etkisi olabilir, fakat bunun daha büyük deneysel çalışmalarla araştırılması gerekir.

ANAHTAR SÖZCÜKLER: Yapışıklık, Diskektomi, Epidural, Fibrozis, Laminotomi

INTRODUCTION

The formation of peridural fibrosis after lumbar laminotomy and discectomy is correlated with the area of surgical dissection, and it occurs equally both anterior and posterior to the nerve roots (27). Peridural fibrosis consists of the formation of extradural fibrous tissue, which causes the dura mater and the nerve roots to adhere to the erector muscles of the spinal column in the posterior part and to the disc and to the vertebral body in the anterior part (25).

The clinical significance of the scar size and development remains controversial (23). A relationship between extensive peridural fibrosis and increased low back pain and/or recurrent radicular pain has been reported (16,22), and the presence of peridural fibrosis has been described in up to 24% of patients with failed back surgery syndrome (3).

The acquisition of meticulous hemostasis is an effective surgical technique for reducing epidural fibrosis. In addition to the development of meticulous surgical techniques, many types of materials have been tested in the epidural space in an effort to reduce scar formation (11). However, the interposition materials that have been used in humans to prevent scar formation, such as gelfoam and fat grafts (9,15), have only addressed posterior scar formation and do little to inhibit anterior fibrosis (27).

Numerous experimental studies on the prevention of postlaminectomy epidural scar formation have been reported (9,15,28). To date, however, there have been few experimental studies on the prevention of scar formation anterior to the dura and the nerve root following discectomy (2, 26, 27).

Recently, carboxymethylcellulose (CMC) and polyethylene oxide (PEO) have been shown to reduce adhesions and to interact with the proteins that cause fibrosis (6,8,12). In 2002, a synthetic combination of CMC/PEO was stabilized with calcium chloride and distributed under the trade names Oxiplex/SP adhesion barrier gel (DePuy International Ltd., Leeds, United Kingdom) and MediShield adhesion barrier gel (Medtronic International Trading SARL, Tolochenaz, Switzerland) in Europe (1).

Studies of laminotomies in rabbits have demonstrated that gels of CMC/PEO (Oxiplex/SP Gel) reduced epidural fibrosis and did not impair normal healing (14, 20, 21). To the best of our knowledge, the use of CMC/PEO gel after disc injury has not been studied in an experimental model. The purpose of this prospective, randomized, experimental study was to investigate whether MediShield has protective effect against anterior scar formation.

MATERIAL and METHODS

Thirty New Zealand White rabbits, each weighing 1650 to 2100 g, were used in this study. The study was approved by the Institutional Animal Investigation Ethics Committee of the Faculty of Pharmacy, Aegean University, Izmir, Turkey. Animals were randomized into the MediShield or control groups using sequentially numbered, opaque sealed envelopes containing the treatment assignments. The treatment assignments were written by a person who was not involved in the study using a random number table. The animals were acclimated to the animal research laboratory for ten days and fed a standard diet prior to the procedure.

The rabbits were sedated by intramuscular injection of 50 mg/kg ketamine (Ketalar, Eczacibasi, Istanbul, Turkey) and 5 mg/kg xylazine (Alfazyne, Egevet, Izmir, Turkey); 100 mg/20 mg intramuscular sulfamethoxazole/trimethoprim (Co-trimoxazole, Egevet, Izmir, Turkey) was administered as an antibiotic. The surgical instruments were disinfected in 4% chlorhexidine gluconate solution (Klorhex, Drogsan, Ankara, Turkey) for 30 minutes prior to the surgery. The animals' were placed on the operating table in the prone position, and their backs were shaved. All subsequent steps were performed by an operator who was wearing sterile surgical gloves The region was scrubbed with 10 % povidone iodine. The skin incision was performed at the midline. Connective tissue and paraspinal muscles were dissected on the left side. Hemostasis was obtained mainly by applying pressure with a surgical cotton and/or gauze. After this stage, a free-standing illuminated magnifying glass was used to magnify the surgical area. A left-sided hemilaminotomy of approximately 5 mm × 10 mm was performed at levels estimated to be L5-L6. The laminotomy and removal of the ligamentum flavum was performed with drill and a thin foot-plated bone punch. The dura was exposed, and the annulus was identified (Figure 1). Hemostasis was obtained by applying a hemostatic gelatin sponge. The sponges were removed after achieving hemostasis. A 21-gauge needle attached to a syringe was inserted into the dorsolateral portion of the annulus fibroses to a depth of approximately 0.5 centimeters, rotated 360°, and then removed.

At this stage, the sealed envelope was opened to reveal the allocation information, and either approximately 0.1 cc MediShield adhesion barrier gel (Medtronic International Trading SARL, Tolochenaz, Switzerland) or nothing was applied to the operation field covering the disc and dura. A standard closure was performed for all animals. Postoperatively, the rabbits were housed in individual cages and allowed to resume normal activity.

Six rabbits died either perioperatively, mostly because of venous bleeding from epidural veins, or less than two months after surgery, mostly because of neurological deficits. Two months after surgery, the living animals (twenty-four rabbits) were euthanized, and their lumbar spines were removed en bloc for pathological evaluations. The actual discectomy level was determined during en bloc excision.

Histological Examination

The en bloc specimens included laminectomy and discectomy fields and were fixed in 10% formaldehyde solution for two

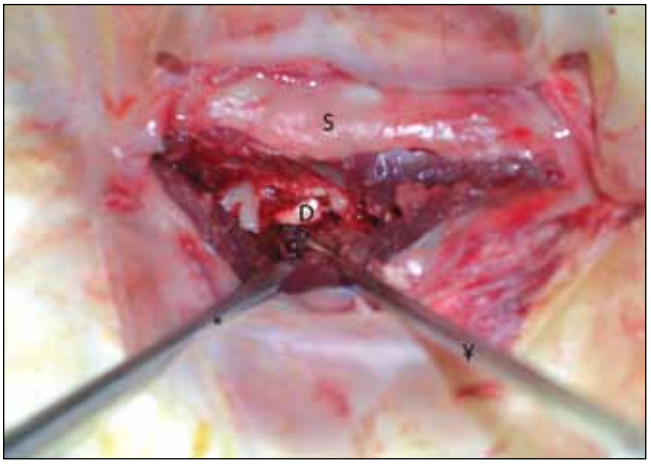

Figure 1: An operative photo showing the left posterolateral region of the rabbit lumbar spinal column after hemilaminotomy. The paravertebral muscles were retracted by Penfield elevator (*) and by suction tube (¥). (S: Spinous process, D: Dura).

days. Each specimen was decalcified in a 5% formic acid solution during a two-week period and then embedded in paraffin. The five-micrometer sections were stained with hematoxylin and eosin (H & E) and Masson's trichrome for light microscopic examination. Five specimens could not be prepared properly and were lost to histological examination. Epidural fibrosis was assessed in 19 rabbit specimens.

All specimens were evaluated by the same pathologist (T.R.) who was blinded to the treatment that had been used. Scar formation was evaluated as present or absent. No grading system was used for two main reasons: there is no validated grading system for scar formation, and — more importantly — the relatively small numbers of rabbits in our groups were better analyzed by statistical tests using nominal data rather than ordinal or continuous data.

Statistical Tests

Fisher's Exact Test was used to compare the MediShield group with the control group. A p value smaller than 0.05 was considered significant.

RESULTS

The 19 histologically examined specimens are summarized in Table I. No superficial or deep infection or complications in the surgical wounds were observed in the 19 rabbits available for follow-up. The MediShield group included 12 rabbits, and the control group included seven rabbits. Epidural fibrosis was found in two out of twelve cases (17%) in the MediShield group (Figure 2A, B) and in three of seven (43%) cases in the control group (Figure 3A, B). Although statistically insignificant (P=0.305, Fisher's Exact Test), this difference was notable.

Table I: Histological Examination Data

No	Actual level	Procedure	Fibrosis
1	L3-L4	MediShield	Absent
2	L4-L5	MediShield	Absent
3	L5-L6	MediShield	Present
4	L5-L6	Control	Present
5	L4-L5	MediShield	Present
6	L5-L6	MediShield	Absent
7	L5-L6	MediShield	Absent
8	L4-L5	MediShield	Absent
9	L6-L7	Control	Absent
10	L3-L4	Control	Present
11	L4-L5	MediShield	Absent
12	L5-L6	Control	Absent
13	L4-L5	MediShield	Absent
14	L6-L7	MediShield	Absent
15	L4-L5	Control	Absent
16	L4-L5	Control	Absent
17	L4-L5	MediShield	Absent
18	L5-L6	Control	Present
19	L5-L6	MediShield	Absent

DISCUSSION

Failed back surgery after lumbar disc herniation occurs in 5-10% of cases (4,28). Some authors have suggested that the formation of postoperative epidural fibrosis with nerve root entrapment and dural compression is the most common cause of surgical failure (5), but attempts at scar excision have produced poor results (18). Scar formation is also a major problem in cases in which second surgery is needed. It was reported that fewer than two-thirds of patients who undergo a repeated lumbar disc operation experience symptom improvement (7). The chance of long-term surgical success after a repeated operation may be diminished in cases with prominent epidural fibrosis (7). Because no effective medical or surgical therapy for peridural fibrosis is currently available (14), many authors have suggested that the prevention of postoperative adhesions is an essential goal for lumbar disc surgery (4). In addition to the acquisition of meticulous hemostasis, the preservation of the ligamentum flavum seems to be beneficial in reducing epidural scar tissue (19). A number of synthetic materials have also been tested as means of controlling epidural fibrosis after lumbar disc surgery (17); however, none has proved consistently effective in clinical practice (1). The only synthetic material that has demonstrated clinical effectiveness is a gel of water-soluble sugars (ADCON-L; Gliatech, Cleveland, OH). However, several reports indicated that this material presented a risk of cerebrospinal fluid leakage in clinical usage (13). Because of these complications, this material is no longer commercially available in some countries (1).

More recently, carboxymethylcellulose (CMC) and polyethylene oxide (PEO), which have been shown to reduce adhesions and to interact with the proteins causing fibrosis, respectively, have given surgeons hope that postlaminectomy outcomes can be improved (6,8,12). Clinical studies seem to encourage this hope (1,10).

Kim KD et al. evaluated the safety of Oxiplex/SP Gel in reducing postoperative epidural fibrosis and related symptoms after surgery for herniated lumbar disc at L4–L5 or L5–S1 in a randomized, single-blind, multicenter, pilot clinical trial study. The treated patients received sufficient (1–3 mL) Oxiplex/SP Gel (CMC/PEO) to coat the nerve root and fill the epidural space. The control condition was surgery alone. The patients completed self-assessment questionnaires concerning leg pain, lower extremity weakness, functional disability, daily living activities, symptoms, and radiculopathy at baseline and at 30 days, 90 days, and six months after surgery. The surgical procedures were well tolerated by the 23 patients treated with Oxiplex/SP Gel and by the 11 control patients. Among patients who had reported significant leg pain and weakness at baseline (11 patients treated with Oxiplex/SP Gel and seven control patients), greater reductions in outcome measures in the Oxiplex/SP Gel group compared with the control group were observed throughout the study (10).

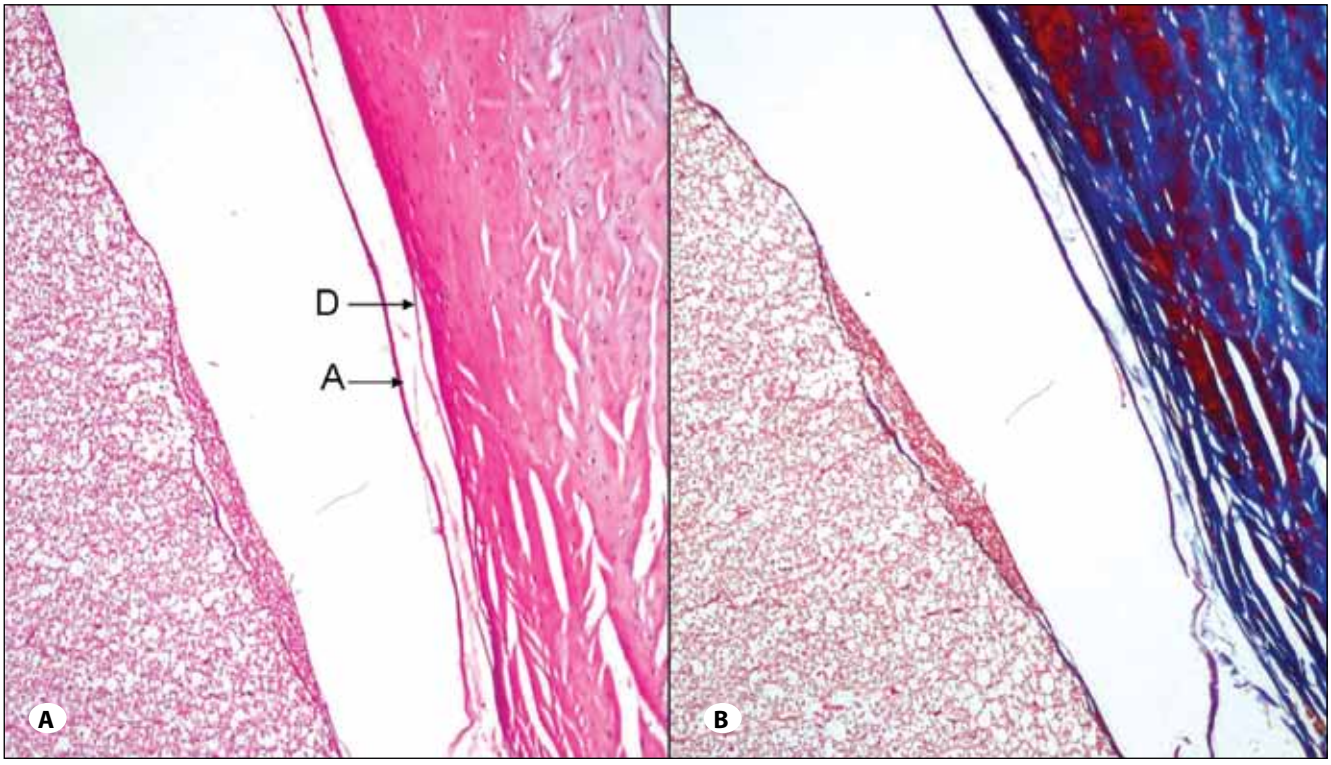

Figure 2: The histological appearance of a discectomy site in the MediShield group. Minimal fibrosis with no dural adhesion was observed. (**A**: Hematoxylin & eosin, 200×; **B**: Masson's trichrome, 200×) (A: Arachnoid mater, D: Dura).

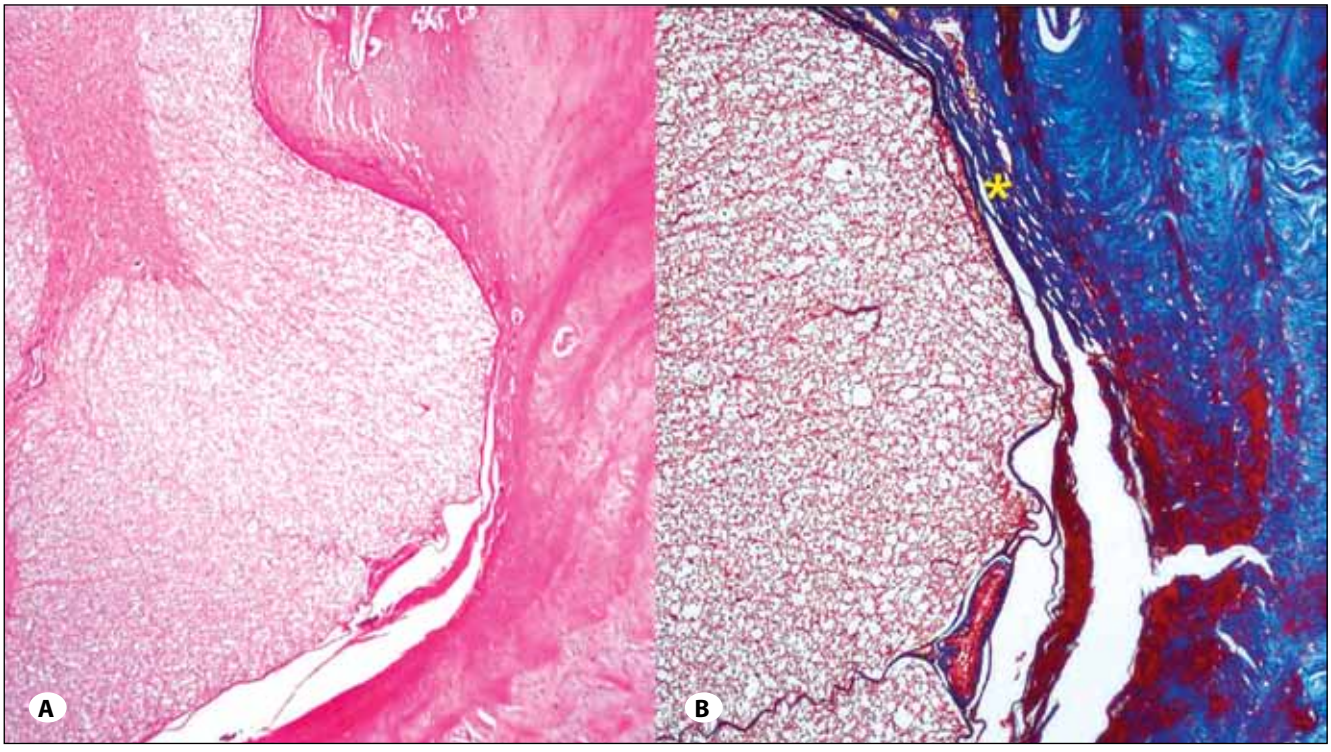

Figure 3: Epidural fibrosis with prominent dural adhesion (asterisk) in the control group (**A**: Hematoxylin & eosin, 200×; **B**: Masson's trichrome, 200×).

Assietti treated a consecutive series of 70 patients with lumbar disc herniation with either CMC/PEO gel (N=35) or no gel (N= 35) at the end of microdiscectomy. The Oswestry disability index (ODI) and leg and back pain scores determined by visual analog scales (VAS) were assessed prior to surgery and at three years postsurgery. The reduction in disability at three years postsurgery, as measured by the decrease in ODI compared with the presurgery value (mean±SD), was significantly greater in the CMC/PEO group than in the control group (-49.4±12.7 vs.-41±17.8). Leg pain, as measured by the decrease in VAS scores at three years postsurgery, were reduced in the CMC/PEO group compared with controls (-6.8 ±1.7 vs. -5.6±1.6). These results indicated that the use of CMC/PEO gel after microdiscectomy with interlaminectomy appears to be safe and significantly reduces disability and leg pain scores compared with conventional treatment in a three-year follow-up (1).

Rhyne et al. recently evaluated the effectiveness of CMC/PEO (Oxiplex) gel for the reduction of pain and associated symptoms after lumbar discectomy in a prospective, randomized, blinded, multicenter clinical trial. Patients undergoing single-level lumbar discectomy by laminectomy or laminotomy were randomized to receive either surgery plus Oxiplex gel (treatment group, n=177) or surgery alone (control group, n=175) and then assessed 6 months after surgery. Significantly more subjects in the surgery-only control group reported dissatisfaction with their self-care (P = 0.04) and ability to perform housework (P = 0.03) compared with subjects in the Oxiplex gel-treated group. Additionally, among patients with substantial back pain at baseline (n = 78), there was a statistically significant reduction of leg pain (P = 0.01) and back pain (P = 0.01) in the treatment group compared with controls (n = 78). Moreover, among patients with severe baseline back pain, the mean overall satisfaction was significantly higher in the Oxiplex gel-treated group (n = 89) compared with the control group (n = 98) (P = 0.04) (24).

Here, carboxymethylcellulose (CMC) and polyethylene oxide (PEO) gel has been used in a rabbit laminectomy model. Rodgers et al. studied barriers comprised of carboxymethylcellulose (CMC) and polyethylene oxide (PEO) (Oxiplex; FzioMed, Inc., San Luis Obispo, CA) as a means to reduce epidural adhesion formation in rabbit laminotomy and laminectomy models. Gels of CMC/PEO containing 10% PEO were most effective among the formulations tested, producing minimal or no epidural fibrosis in up to 84% laminotomy sites, whereas controls exhibited epidural fibrosis in over 90% of sites. These authors reported that a barrier composed of either a viscous gel of CMC/PEO alone or a gel/film combination is effective in preventing epidural fibrosis in a rabbit model of postsurgical adhesions (21). Rodgers et al. also showed that the use of an Oxiplex/SP Gel reduced epidural fibrosis without affecting dural healing, even in the presence of a large dural incision in another rabbit laminectomy model (20).

Kurt et al. have shown that Oxiplex and Gore-Tex share a similar barrier effect. Both products successfully prevent the formation of peridural fibrosis in an experimental model of laminectomy. These authors proposed that both Oxiplex and Gore-Tex might be used safely to prevent peridural fibrosis (14).

Though it was not statistically significant, we observed a difference between the MediShield and control groups that favored the MediShield group, similar to previous studies. One difference between our rabbit model and previous studies is that we made a disc puncture. To our knowledge, a disc injury model has not been studied in rabbits to investigate epidural fibrosis before. We aimed to simulate the hemilaminotomy-discectomy procedure in an experimental rabbit study.

The between-group difference observed in our study might have been non-significant because of the small numbers of subjects (possibility of a type II error because of small n). The application of a CMC/PEO gel (MediShield) might have a positive effect on the prevention of the epidural fibrosis after lumbar discectomy, but this should be investigated further in larger experimental trials.

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