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Post-cataract Prevention of Inflammation and Macular Edema by Steroid and Nonsteroidal Anti-inflammatory Eye Drops

A Systematic Review

Line Kessel, MD, PhD,[1,2] Britta Tendal, PhD,[2] Karsten Juhl Jørgensen, MD, DrMedSci,[2,3] Ditte Erngaard, MD,[4] Per Flesner, MD, PhD,[5] Jens Lundgaard Andresen, MD, PhD,[6] Jesper Hjortdal, MD, DrMedSci[7]

Purpose: Favorable outcome after cataract surgery depends on proper control of the inflammatory response induced by cataract surgery. Pseudophakic cystoid macular edema is an important cause of visual decline after uncomplicated cataract surgery.

Design: We compared the efficacy of topical steroids with topical nonsteroidal anti-inflammatory drugs (NSAIDs) in controlling inflammation and preventing pseudophakic cystoid macular edema (PCME) after uncomplicated cataract surgery.

Participants: Patients undergoing uncomplicated surgery for age-related cataract.

Methods: We performed a systematic literature search in Medline, CINAHL, Cochrane, and EMBASE databases to identify randomized trials published from 1996 onward comparing topical steroids with topical NSAIDs in controlling inflammation and preventing PCME in patients undergoing phacoemulsification with posterior chamber intraocular lens implantation for age-related cataract.

Main Outcome Measures: Postoperative inflammation and pseudophakic cystoid macular edema.

Results: Fifteen randomized trials were identified. Postoperative inflammation was less in patients randomized to NSAIDs. The prevalence of PCME was significantly higher in the steroid group than in the NSAID group: 3.8% versus 25.3% of patients, risk ratio 5.35 (95% confidence interval, 2.94 9.76). There was no statistically significant difference in the number of adverse events in the 2 treatment groups.

Conclusions: We found low to moderate quality of evidence that topical NSAIDs are more effective in controlling postoperative inflammation after cataract surgery. We found high-quality evidence that topical NSAIDs are more effective than topical steroids in preventing PCME. The use of topical NSAIDs was not associated with an increased events. We recommend using topical NSAIDs to prevent inflammation and PCME after routine cataract surgery. *Ophthalmology 2014;121:1915-1924 © 2014 by the American Academy of Ophthalmology.*

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Cataract surgery is one of the most frequently performed elective surgical procedures in developed countries. The surgical methods have improved significantly over the years, thus lowering the risk of complications and raising patients' and surgeons' expectations of a successful visual outcome. In patients without other eye diseases, 20/20 visual outcome is a realistic expectation.

Like other types of surgery, cataract surgery induces a surgical inflammatory response. Uncontrolled inflammation may lead to serious side effects, such as posterior synechia, uveitis, and secondary glaucoma. Management of inflammation is thus a mainstay in modern cataract surgery. Currently, 2 drug groups are available to control ocular inflammation: steroids and nonsteroidal anti inflammatory drugs (NSAIDs). Steroids are potent anti inflammatory agents that work by acting on a number of intercellular inflammatory mediators, and NSAIDs work by inhibiting the cyclooxygenase enzymes. The cyclooxygenase enzymes catalyze the formation of prostaglandins and thromboxanes. Prostaglandins mediate inflammatory reactions. Preventing the formation of prostaglandins reduces the inflammatory process.

Pseudophakic cystoid macular edema (PCME, also termed "Irvine Gass syndrome") is a swelling of the fovea due to fluid accumulation occurring a few weeks to months after cataract surgery. It is the most common cause of visual decline after cataract surgery. The prevalence of PCME varies from study to study depending on how PCME is defined. By using fluorescein angiography, a prevalence of PCME of up to 20% has been reported,[1,2] whereas only 2% were diagnosed with PCME when loss of visual acuity was required to establish the diagnosis.[1,3] Usually, PCME is

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subclinical and self-limiting, but in a few patients it may become chronic, resulting in permanent visual loss.

The cause of PCME is thought to be an increased vascular permeability induced by inflammatory mediators such as prostaglandins. Some reports have found an increased risk of PCME in patients using prostaglandin analogs to control glaucoma.[4,5] There is a tendency toward a higher prevalence of PCME in patients with increased postoperative inflammation.[2] The relationship between inflammation and PCME is further supported by the 3-fold increase in the risk of PCME in patients with a history of uveitis.[6] Macular thickness is greater in patients with complicated cataract surgery compared with uncomplicated surgery.[7] Increased surgical trauma such as iatrogenic iris lesion increases the risk of PCME.[1] Furthermore, the risk of PCME is increased in patients with a history of retinal venous occlusion or an epiretinal membrane,[3] whereas posterior vitreous detachment seems to protect against PCME.[1]

Deciding which anti-inflammatory agent to use as standard in patients undergoing cataract surgery is important to ensure a favorable outcome. The present systematic review compares the efficacy of topical steroids with that of topical NSAIDs in reducing postoperative inflammation and preventing PCME. The study was initiated by the Danish Health and Medicines Authorities to formulate evidence-based national guidelines on the management of age-related cataract.

Sources and Methods of Literature Search

We performed this systematic review and subsequent meta analyses on the basis of the principles described in the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[8] We first defined the topic of the systematic review using the Patient, Intervention, Comparison, and Outcome approach.[9] We compared the efficacy of steroid eye drops (Intervention) with NSAID eye drops (Comparison) in preventing inflammation (Outcome) and PCME (Outcome) after uncomplicated cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation in patients with age related cataract (Patients). We included only randomized controlled trials in the meta analysis. We excluded references comparing other types of interventions or surgical methods. We did not compare the additive effects of steroids plus NSAIDs versus steroids or NSAIDs alone because a Cochrane protocol covers this topic.[10] We included all types of topical steroids and topical NSAIDs in the review.

For outcomes, we analyzed the number of cells and flare as inflammation markers measured by laser flare cell photometry or slit lamp evaluation, PCME as defined in the included studies (fluorescein angiograms or optical coherence tomography [OCT]), and best corrected distance visual acuity at last follow up after cataract surgery. The time point for evaluation of inflammation was at 2 to 8 days post surgery. The time point for evaluation of PCME was as chosen by the included studies. Risks and adverse events associated with the use of topical eye drops were also quantified using the number of complications as defined in the included studies and the intraocular pressure (IOP) after the treatment period.

We performed a systematic literature search in April 2013 in the EMBASE, Medline (Ovid), Cochrane Library, and CINAHL databases. An example of the search strategy for the EMBASE database is provided in Appendix 1 (available at www.aaojournal.org). Similar search strategies were used for the other databases. The search was limited to references published from 1996 and onward in the English or Scandinavian languages. The year limitation was chosen to ensure that only studies using surgical methods that were comparable to modern date methods were included. The literature search was performed by a trained information specialist (Birgitte Holm Pedersen). We did not search trial registries for unpublished trials. According to Danish law, no institutional review board approval was required for the study.

We assessed the risk of bias of each included study using the Cochrane risk of bias tool[11] in the Review Manager Software (Review Manager [RevMan] version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012, available at: http://tech.cochrane.org/revman/download, Accessed April 2013). In short, the Cochrane risk of bias tool assesses risk of bias associated with the selection of patients (randomization or patient allocation and concealment of allocation), study performance (blinding of patients and personnel), measurement of outcomes (blinding of outcome assessment), attrition of data (e.g., missing patients or dropouts), reporting of study findings (selective outcome reporting), or other types of bias related to the study design that could affect the internal validity. This part of the systematic review was done independently by 2 reviewers (BT and KJJ). Disagreement was resolved through discussion and consensus.

We evaluated the quality of the evidence for each prespecified outcome across the included studies using the GRADE system in the Grade Profiler Software (version 3.6, 2011, available at: http://tech.cochrane.org/revman/other resources/gradepro/download, Accessed April 2013). We analyzed each outcome for study limitations that could affect the outcome (i.e., risk of bias),[12] inconsistency (different results between studies),[13] indirectness (was the study population and intervention comparable to the patient population and intervention that is relevant to users [external validity], use of surrogate measures),[14] imprecision (large confidence intervals [CIs] or the lack of statistical strength),[15] and risk of publication bias (small number of studies or included patients, lack of reporting of negative findings).[16] We upgraded or downgraded the quality of the evidence for each of the prespecified outcomes on the basis of the assessment of each of the limitations mentioned earlier.

We analyzed continuous outcome data using mean difference and dichotomous outcome data using risk ratios. We used the Review Manager 5 Software to calculate estimates of overall treatment effects and random effects models to calculate pooled estimates of effects.

Summary of Evidence

Our systematic literature search returned 352 titles and abstracts, and 82 references were identified by other sources. Titles and abstracts were reviewed by 1 reviewer (LK), and 115 references were judged to be of potential interest by the reviewer. These were collected in full text, and 15 randomized controlled clinical trials met our inclusion criteria.[17 31] All included studies excluded patients with ocular diseases (e.g., glaucoma, uveitis, previous surgery, or trauma), which might affect the outcome after surgery. Seven of the included trials compared the prophylactic effect of topical steroids and NSAIDs on the occurrence of cystoid macular edema after cataract surgery.[17,25 28,31]

Table 1. Overview of Interventions in Included Studies

Study ID	Steroid	NSAID	Dosing
Asano et al 2008[17]	Betamethasone sodium 0.1%	Diclofenac sodium 0.1%	1 drop 3 hrs, 2 hrs, 1 hr, and ½ hr preoperatively and then 3×/day for 8 wks
Demco et al 1997[18]	Prednisolone acetate 1.0%	Diclofenac sodium 0.1%	4×/day from the first postoperative day
El-Harazi et al 1998[19]	Prednisolone acetate 1%	Diclofenac sodium 0.1%	4×/day from the first postoperative day for 1 wk, then 2×/day for 3 wks
El-Harazi 1998 (steriod B)[19]	Prednisolone acetate 1%	Ketorolac tromethamine 0.5%	4×/day from the first postoperative day for 1 wk, then 2×/day for 3 wks
Endo et al 2010[20]	Betamethasone sodium phosphate for 1 wk and fluorometholone 0.1% for 5 wks	Bromfenac	Steroid group: 4×/day for 5 wks NSAID group: 2×/day for 5 wks
Hirneiss et al 2005[21]	Prednisolone acetate 1%	Ketorolac tromethamine 0.5%	6 drops/day on days 1–3, 5 drops/day on days 4–10, 4 drops/day on days 11–14, 3 drops/day on days 15–18, 2 drops/day on days 19–21, 1 drop/day on days 22–28
Hirneiss et al 2005 B[21]	Rimexolone 1%	Ketorolac tromethamine 0.5%	6 drops/day on days 1–3, 5 drops/day on days 4–10, 4 drops/day on days 11–14, 3 drops/day on days 15–18, 2 drops/day on days 19–21, 1 drop/day on days 22–28
Holzer et al 2002[22]	Loteprednol etabonate 0.5%	Ketorolac tromethamine 0.5%	1 drop 4×/day the first week after surgery, then 1 drop 2×/day for the remainder of the study
Laurell and Zetterstrom 2002[23]	Dexamethasone phosphate 0.1%	Diclofenac sodium 0.1%	4×/day the first week, then 2×/day for 3 wks
Missotten et al 2001[24]	Dexamethasone 0.1%	Indomethacin 0.1%	4×/day beginning the day before surgery and for 30 days postoperatively
Miyake et al 2000[28]	Fluorometholone 0.1%	Diclofenac 0.1%	1 drop 3 hrs, 2 hrs, 1 hr, and ½ hr before surgery, then 3×/day for 8 wks
Miyake et al 2007[27]	Fluorometholone 0.1%	Diclofenac 0.1%	1 drop 3 hrs, 2 hrs, 1 hr, and ½ hr before surgery, then 3×/day for 5 wks
Miyake et al 2011[26]	Fluorometholone 0.1%	Nepafenac 0.1%	3×/day starting the day before surgery until 5 wks postoperatively
Miyanaga et al 2009[25]	Betamethasone 0.1% for 1 mo, then fluorometholone 0.1% for 1 mo	Bromfenac 0.1%	Steroid group: 4×/day for 8 wks NSAID group: 2×/day for 8 wks
Roberts and Brennan 1995[29]	Prednisolone acetate 1%	Diclofenac 0.1%	4×/day for 1 wk, then 2×/day for 3 wks
Solomon et al 2001[30]	Rimexolone 1%	Ketorolac tromethamine 0.5%	4×/day beginning immediately after surgery
Wang et al 2013[31]	Fluorometholone 0.1%	Bromfenac sodium 0.1%	Steroid group: 3×/day for 1 mo NSAID group: 2×/day for 1–2 mos
Wang et al 2013 B[31]	Dexamethasone 0.1%	Bromfenac sodium 0.1%	Steroid group: 3×/day for 1 mo NSAID group: 2×/day for 1–2 mos

NSAID nonsteroidal anti-inflammatory drug.

Characteristics and risk of bias assessments of the included studies are provided in Appendix 2 (available at www.aaojournal.org). A list of excluded studies with reasons for exclusion is provided in Appendix 3 (available at www.aaojournal.org).

The included studies compared different types of steroids with different types of NSAIDs. Table 1 provides an overview of the included interventions and comparisons.

Prevention of Inflammation

The anti-inflammatory effect of topical NSAIDs and steroid eye drops after cataract surgery was evaluated by examining signs of intraocular inflammation: cells and flare. Some studies used laser cell-flare photometry, and others used a slit-lamp to identify inflammatory signs. Those studies that used a slit-lamp did not consistently use comparable grading systems, which made their inclusion in a meta-analysis difficult. For this reason, we chose to include only studies evaluating inflammation by laser cell-flare photometry in our meta-analysis. All included studies used a study design in which patients with a history of ocular inflammation (iritis or uveitis) had been excluded from the study.

Inflammation Measured as Number of Cells

Only 4 of the included studies reported on the number of cells as evaluated by laser cell-flare photometry. We did not

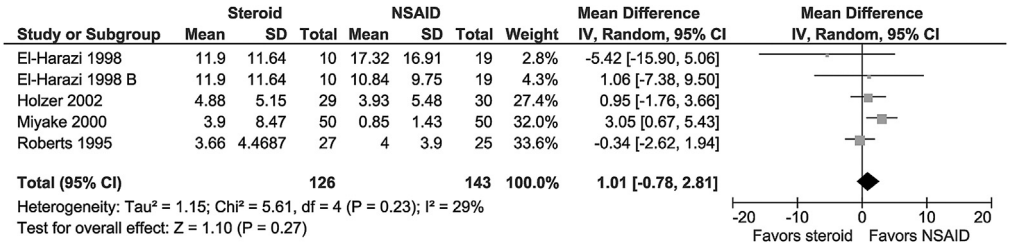

Figure 1. Forest plot comparing the effect of topical steroid versus nonsteroidal anti-inflammatory drug (NSAID) eye drops on inflammation quantified as the number of cells detected by laser cell-flare photometry (photons/ms) at 1 week postoperatively. CI confidence interval; df degrees of freedom; IV inverse variance; SD standard deviation.

find a significant difference in the number of cells detected by laser cell-flare photometry at 1 week postoperatively between patients randomized to steroid or NSAID eye drops. The mean difference was 1.01 (95% CI, −0.78 to 2.81; I^2 29%). All 4 studies used steroid eye drops of low to medium potency: prednisolone,[19,29] loteprednol,[22] or fluorometholone.[28] The meta-analysis is shown in Figure 1.

Inflammation Measured as Flare

We found that topical NSAIDs were more effective than steroid eye drops in reducing postoperative inflammation measured as the amount of flare by laser flare photometry at 1 week postoperatively. The mean difference was 6.88 (95% CI, 3.26 10.50; I^2 89%). However, steroids of medium to high potency (betamethasone, dexamethasone, loteprednol, and prednisolone) were not significantly different from NSAIDs in controlling inflammation, whereas steroids of low potency (fluorometholone) were significantly less effective in controlling inflammation (Fig 2).

Pseudophakic Cystoid Macular Edema

We identified 7 randomized clinical trials that compared the prevalence of PCME after topical steroid or NSAID.[17,20,25 28,31] One of the 7 studies reported foveal thickness measured by OCT in patients with diabetes mellitus and was excluded from the analysis of PCME.[20] Thus, all 6 studies included in this meta-analysis used a study design in which patients with a history of uveitis, diabetes, or diabetic retinopathy were excluded from participation. Four studies evaluated the presence of PCME by fluorescein angiography 5 weeks after cataract surgery.[17,26 28] The remaining 2 studies evaluated the presence of PCME by

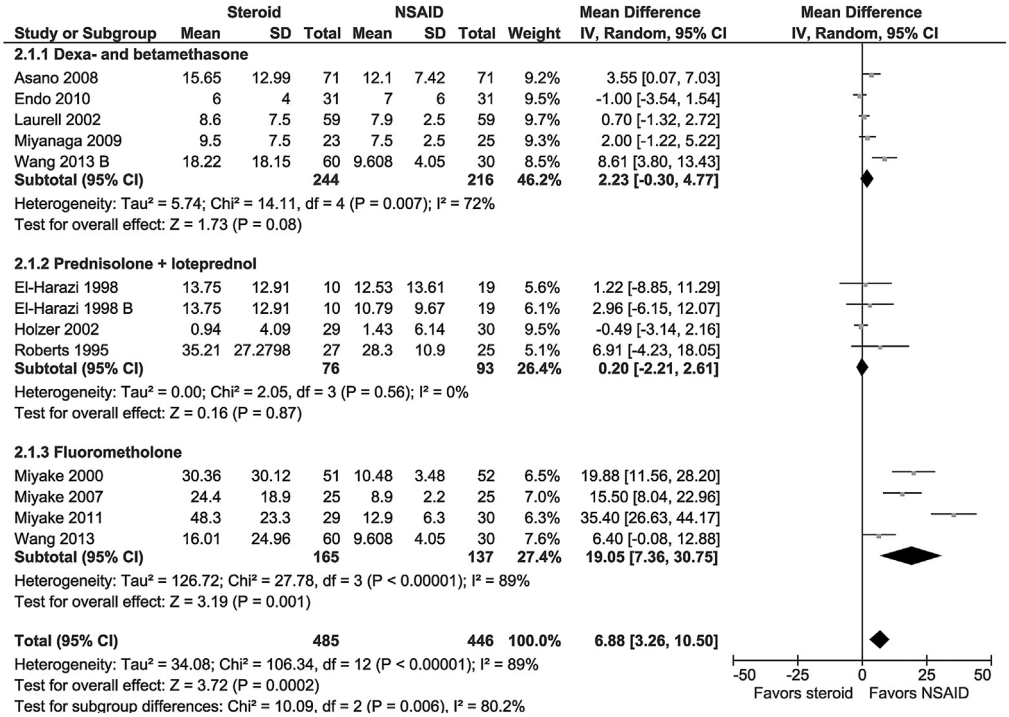

Figure 2. Topical steroid versus nonsteroidal anti-inflammatory drug (NSAID) eye drops on preventing postoperative inflammation quantified by laser flare photometry (photons/ms) at 1 week after cataract surgery. CI confidence interval; df degrees of freedom; IV inverse variance; SD standard deviation.

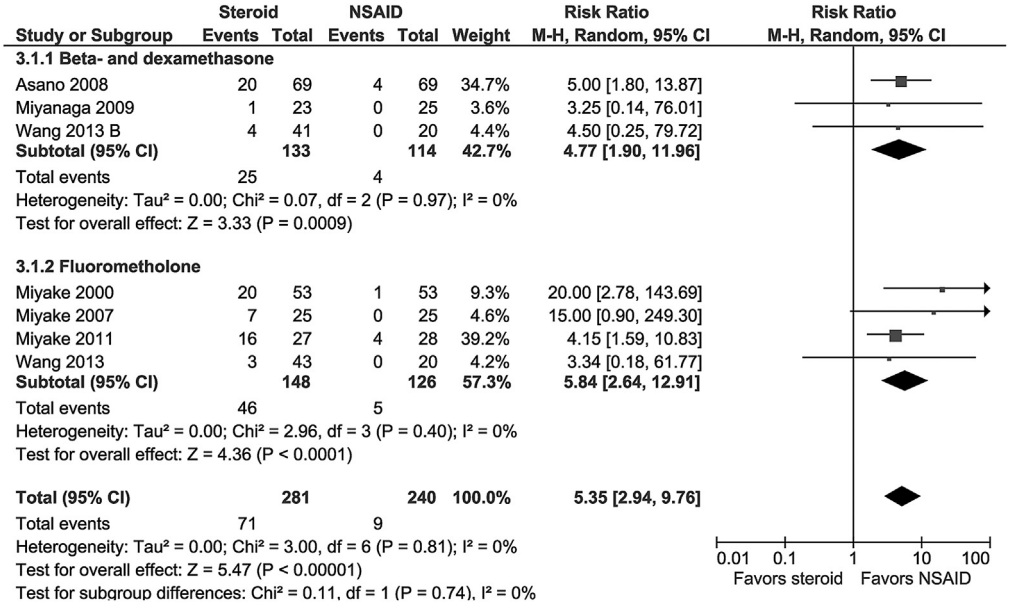

Figure 3. Topical steroid versus nonsteroidal anti-inflammatory drug (NSAID) for preventing cystoid macular edema at 1 month after cataract surgery. CI confidence interval; df degrees of freedom; M-H Mantel–Haenszel.

OCT 1 month after cataract surgery.[25,31] Some of the patients received highly potent steroids (betamethasone or dexamethasone),[17,25,31] whereas others received a less potent steroid (fluorometholone).[26–28] In the steroid group, 25.3% of patients had PCME at 1 month versus 3.8% in the NSAID group (risk ratio, 5.35; 95% CI, 2.94 9.76; I^2 0%). Potent and weaker steroids were both less effective than NSAIDs, and there was no indication that potent steroids were more effective than weaker steroids ($P = 0.74$, test for subgroup difference) (Fig 3).

Visual Acuity after Cataract Surgery

Four studies reported the visual acuity at the longest follow-up 6 to 8 weeks after cataract surgery.[17,20,25,31] Best-corrected distance visual acuity was on average 0.02 logarithm of the minimum angle of resolution (95% CI, −0.01 to 0.05; I^2 72%) better in the NSAID group compared with the steroid group. This corresponds to 1 letter on the Early Treatment of Diabetic Retinopathy Study chart. The difference was not statistically significant ($P = 0.19$) (Fig 4).

Risks and Adverse Events

Both topical steroids and topical NSAIDs can be associated with harms. Twelve of the included studies reported the number of harms in both treatment groups.[17,19,21,24,26,28,31] Harms ranged from bitter taste to uveitis with hypopyon, but the majority of harms were simply reported as "complications" without further description. We evaluated the number of harms as reported in the included studies in addition to study withdrawals due to harms of the treatment. The overall prevalence of harms was 5.5% in the steroid group and 6.6% in the NSAID group. The difference was not significant (risk ratio, 0.76; 95% CI, 0.50 1.15; I^2 0%) (Fig 5).

Nonsteroidal anti-inflammatory drugs have been associated with corneal melts, and although all patients had an anterior segment slit-lamp examination postoperatively, none of the studies specifically reported melts; thus, we could not perform a meta-analysis for complications specifically related to NSAID use.

Steroids are known to be associated with a risk of increased IOP. As shown in Figure 6, patients who were

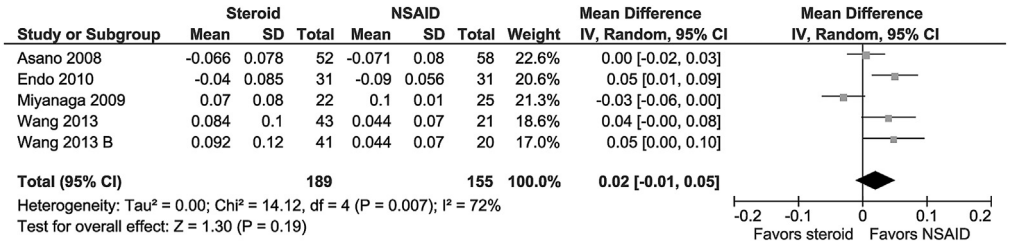

Figure 4. Final visual acuity (logarithm of the minimum angle of resolution [logMAR]) at the last follow-up 6 or 8 weeks after cataract surgery in patients randomized to topical steroids or topical nonsteroidal anti-inflammatory drug (NSAIDs). CI confidence interval; df degrees of freedom; IV inverse variance; SD standard deviation.

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