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Primary Hip

Intra-Articular Hyaluronic Acid Injections Less Than 6 Months Before Total Hip Arthroplasty: Is It Safe? A Retrospective Cohort Study in 565 Patients

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ABSTRACT

Background: Intra-articular hyaluronic acid (IAHA) can be injected into an osteoarthritic hip joint to reduce pain and to improve functionality. Several studies report IAHA to be safe, with minor adverse effects that normally disappear spontaneously within a week. However, intra-articular corticosteroids prior to total hip arthroplasty (THA) have been associated with increased infection rates. This association has never been investigated for IAHA and THA. We aimed to assess the influence of IAHA on the outcome of THA, with an emphasis on periprosthetic joint infection (PJI).

Methods: At a mean follow-up of 52 months (±18), we compared complication rates, including superficial and deep PJIs, of THA in patients who received an IAHA injection ≤6 months prior to surgery (injection group) with that of patients undergoing THA without any previous injection in the ipsilateral hip (control group). One hundred thirteen patients (118 hips) could be retrospectively included in the injection group, and 452 patients (495 hips) in the control group.

Results: No differences in baseline characteristics nor risk factors for PJI between the 2 groups were found. The clinical outcomes in terms of VAS pain scores (1.4 vs 1.7 points, $P = .11$), modified Harris Hip Scores (77 vs 75 points, $P = .09$), and Hip disability and Osteoarthritis Outcome Scores (79 vs 76 points, $P = .24$) did not differ between the injection group and the control group. Also, complications in terms of persistent wound leakage (0% vs 1.2%, $P = .60$), thromboembolic events (0% vs 0.6%, $P = 1.00$), periprosthetic fractures (1.7% vs 1.2%, $P = .65$), and dislocations (0% vs 0.4%, $P = 1.00$) did not differ. However, in the injection group there was a higher rate of PJIs (4% vs 0%, $P < .001$) and postoperative wound infections (9% vs 3%, $P = .01$), compared to the control group.

Conclusion: Our findings suggest that IAHA performed 6 months or less prior to THA may pose a risk for increased rates of PJI. We recommend refraining from performing THA within 6 months after IAHA administration.

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For patients suffering from hip osteoarthritis (OA), intra-articular injection therapy with corticosteroids (CS) or hyaluronic acid (HA) is generally considered a valid treatment option to relieve pain and to possibly postpone the need for total hip arthroplasty (THA) [1]. Noncomparative studies consistently show satisfactory pain reduction and functional improvement after intra-articular hyaluronic acid (IAHA) [2]. Yet, recent meta-analyses reported contrasting findings, ranging from statistically significant pain reduction to no effect, regarding the efficacy of IAHA in hip OA [1,3,4]. More methodologically sound, adequately powered studies to evaluate intra-articular agents for hip OA are required [1,4,5]. Meanwhile, IAHA may still be used as a nonoperative treatment option for short-term pain relief in hip OA [4].

Intra-articular injections of HA and CS within 3 months prior to knee arthroplasty have been associated with an increased risk of periprosthetic joint infection (PJI) [6]. Several studies have analyzed the effect of previous intra-articular injections of CS on THA infection rates [7]. In early studies there was reason to believe that there was a higher risk of PJIs [8–13]. Yet, a systematic review found that 2 out of 9 (low quality) studies reported an increased infection rate for THA after intra-articular CS, while 7 studies found no effect [7].

To our knowledge, the relationship between IAHA injections in the hip and the outcome of subsequent THA has not yet been studied. Our aim was to assess the potential influence of previous IAHA on the outcome of THA, with a focus on PJI and post-operative wound infections. We retrospectively analyzed the outcome of THA in patients who received an IAHA injection within 6 months prior to surgery and compared these results with a control group of patients who did not have a history of intra-articular injections.

Methods

Patient Selection

The prospectively documented electronic record cards of all patients treated in our center diagnosed with hip OA between January 2005 and December 2009 were screened to identify 2 study groups:

1. Patients who received an IAHA injection in the hip joint less than 6 months before performing THA (injection group).
2. Patients who received THA without any previous intra-articular injection (control group).

The indication for performing an intra-articular injection of the hip with HA was the same for all our patients, namely pain and disability, and a Kellgren and Lawrence grade 2 or 3 OA as shown on the anteroposterior and lateral X-ray [14]. It was discussed with all patients that performing an intra-articular injection was the final conservative treatment option.

The indication to perform a THA after the administration of IAHA depended on the efficacy of the treatment and the patient's expectations. We always discussed the possibility of performing THA if the patient was not satisfied with the efficacy of the IAHA. Ultimately, the patient decided whether or not to undergo the THA operation.

Exclusion criteria included the use of immunosuppressive drugs, a history of malignancy, sero-negative inflammatory arthropathy of the affected hip, previous surgery of the affected hip, intra-articular injection of another product than HA into the affected hip, or infection of the affected hip.

Data Collection

Two researchers reviewed the electronic patient record files and retrieved the information on the baseline characteristics (gender, age at the time of THA, body mass index, American Society of Anesthesia score). Risk factors for the development of PJI for both groups included rheumatoid arthritis, diabetes mellitus, smoking at the time of surgery, and kidney failure (creatinine clearance <60 mL/min) [15,16]. An additional risk factor for the injection group was the time between HA injection and THA, which was assumed to be of interest based on previous studies on CS injection prior to THA [7].

At baseline, the pain, measured with a 100-point Visual Analog Scale (VAS) for pain, and the functionality, measured with the modified Harris Hip Score (mHHS), were determined [17–20]. The mHHS is a self-administered functional score and pain score (without the physical examination part which is included in the original HHS) with a range of 0-91 points. Clinical outcome was determined using the VAS for pain, the mHHS, and the Hip disability and Osteoarthritis Outcome Score (HOOS) [21].

The electronic patient record files, containing prospectively documented patient information, were assessed in order to study the postoperative complications and adverse events of THA. For a PJI, the definition from the workgroup of the Musculoskeletal Infection Society was used [22]. Wound infections were defined as wounds displaying a delayed healing with clinical signs of infection, that is, redness, warmth, persistent wound leakage >1 week postoperatively, with or without positive peroperative or post-operative tissue cultures, and the administration of antibiotics for at least 1 week. In our clinic, cases of persistent wound leakage >1 week after surgery and redness of the skin around the wound were considered wound infections for which oral antibiotics were administered. Other peroperative and postoperative complications were also documented.

All the available medical images (radiographs, computed tomography scans) were studied to find any signs of loosening of the THA.

Final Follow-Up

In December 2011, 2 years after the end of the inclusion period, all patients were contacted by mail. In this letter they received information regarding the study and their consent to use their data was asked. Furthermore, patients were questioned about post-operative problems, including prolonged postoperative use of antibiotics, limping, functional loss, and revision surgery of the affected hip. We used this information to verify the information retrieved from the electronic patient record files. Patients were asked to fill out the VAS for pain, the mHHS, and the HOOS. For patients who did not return the questionnaire we attempted to contact them by phone twice. Five patients in the injection group and 26 in the control group deceased before the end of follow-up in December 2011. Although we intended to have a follow-up of at least 2 years, 3 patients in the injection group (2.7%) and 16 patients in the control group (3.4%) had a follow-up between 1 and 2 years (all of these patients died before 2 years of follow-up). For these patients the data of the last available follow-up visit were used. None of these patients had had a PJI of their THA prior to their death.

Treatment

Patients received full information regarding the treatment options and the potential risks and benefits. Informed consent to perform the intra-articular injection and/or the THA was obtained.

Injection

All IAHA injections were performed in the operating room by the senior author under strict sterile conditions (sterile gown, mask, sterile gloves, and sterile table cover), using a lateral approach and under fluoroscopic guidance. The affected hip was exposed and prepared with polyvidone iodine 10% solution (isoBetadine; Meda Pharma nv., Brussels, Belgium). Layer by layer local anesthesia was performed using lidocaine 1% (Braun Medical NV/SA, Diegem, Belgium). The original and sterile syringe containing HA was given by the nurse just before injection. Through an 18 gauge spinal needle (Becton, Dickinson and Company, Temse, Belgium) the intra-articular injection was performed. Intra-articular positioning of the needle was confirmed using contrast (Ultravist-300; Bayer Pharma AG, Berlin, Germany). After verifying intra-articular needle placement, the hip was infiltrated with HA (Ostenil [1.2-1.4 mDa], TRB Chemedica, Haar, Germany). The patients were allowed immediate weight bearing and were discharged from the hospital at the end of the day.

Total Hip Arthroplasty

The indication for THA is based on the severity of the clinical and radiographic signs of OA. As mentioned, the patient ultimately decided whether a THA was performed or not. The operation was identical in all patients and was performed by the senior author using an anterolateral approach in a supine position in the operating room under laminar airflow. Antibiotic prophylaxis (cefazolin 2 g; Mylan bvba, Hoeilaart, Belgium) was given just before the start and immediately after the operation in 3 doses to ensure antibiotic coverage for 24 hours. The operation was performed under strict sterile conditions. The surgeon was wearing 2 pairs of sterile gloves, a sterile gown, and a sterile surgical helmet. The leg was disinfected using polyvidone iodine 10% solution from the ankle up to the inferior part of the chest. Sterile disposable drapes were used. Only cemented THAs were performed. The cement was loaded with gentamicin in all patients. After performing THA, the wound was closed in layers (the skin intradermal) using one drain beneath the tensor fascia latae muscle, which was always removed within 1 day after the operation. There was sterile wound care every day for at least 1 week or for as long as there was wound leakage. Thrombosis prophylaxis (enoxaparin; Sanofi-Aventis Belgium, Diegem, Belgium) was administered in all patients for 6 weeks postoperatively.

Statistical Analysis

The Fisher's exact test and Mann-Whitney *U*-test were used to compare nominal and continuous variables respectively. The results of these nonparametric tests were reported as main results. However, since 48 patients underwent bilateral operations (45 of them at a different moment in time), the robustness of the conclusions was verified using 2 approaches. First, a statistical technique was applied accounting for the possible correlation between the outcomes. More specifically, a logistic regression model with generalized estimating equations was used for the binary outcome "presence of any complication." Since for all other outcomes (functional scores as well as binary outcomes referring to presence of specific complication) bilateral THA patients showed very low variability in their results between both sides, the aforementioned nonparametric analyses were performed on patient level. In these analyses on patient level, the mean value was used for continuous outcomes if there was a difference between both sides ($N = 0$ for HHS, $N = 2$ for VAS, and $N = 1$ for HOOS). For the binary outcomes with a different value between both sides, the patient was defined as having a complication if at least 1 of the 2 sides presented with a complication. A *P*-value of $<.05$ was considered significant. All analyses were performed using SAS software, version 9.2 of the SAS System for Windows (SAS Institute Inc, Cary, NC).

Ethical Committee Approval

Ethical approval was received from the Ethical Committee of the University Hospitals Leuven (approval# S53672). The data collection and patient contacts were handled according to the ethical standards of the Declaration of Helsinki.

Results

Baseline Characteristics

Between January 2005 and December 2009, 839 intra-articular injections with HA were performed in 441 patients suffering from hip OA. Of those patients, 188 went on to receive THA and 116 did so within 6 months after an IAHA injection (5 bilateral). Three patients (3 hips) were excluded for further analysis because of preoperative presence of one or more exclusion criteria, leaving 118 THAs (113 patients) for analysis (Figure 1).

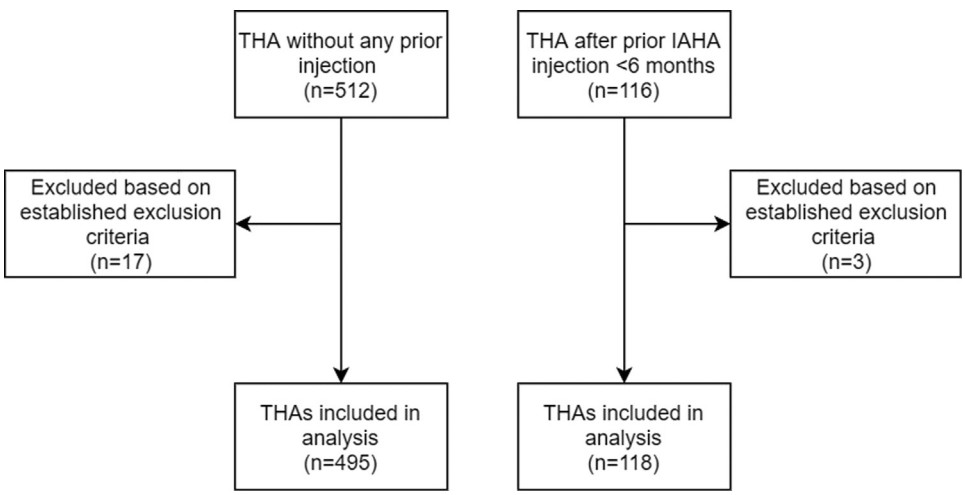

Fig. 1. Inclusion flowchart. IAHA, intra-articular hyaluronic acid; THA, total hip arthroplasty.

Table 1
Demographic Data, Including Risk Factors for Periprosthetic Joint Infections.

Patient Characteristics	Injection Group (n = 118)	Control Group (n = 495)	*P*-Value
Gender, female (%)	72 (64%)	310 (69%)	.37
Age at the time of THA, y (SD)	69.1 ± 8.8	68.2 ± 12.4	.84
Mean follow-up after THA, mo (SD)	50.0 ± 15.5	52.3 ± 17.9	.27
Body mass index, mean (SD)	26.6 ± 3.4	27.2 ± 5.0	.41
ASA preoperative score (%)[a]			.39
ASA = 1	31/118 (26.3%)	110/495 (22.2%)	
ASA >1	87/118 (73.7%)	385/495 (77.8%)	
VAS pain, mean (SD)	6.3 ± 1.7	6.2 ± 1.9	.92
Modified HHS, mean (SD)	47.2 ± 14.8	46.1 ± 14.5	.53
Rheumatoid arthritis (%)	3/118 (2.5%)	8/495 (1.6%)	.45
Diabetes mellitus (%)	7/118 (5.9%)	34/495 (6.9%)	.84
Renal failure (creatinine clearance < 60 mL/min) (%)	2/118 (1.7%)	11/495 (2.2%)	1.000
Smoking (%)	14/118 (11.9%)	68/495 (13.7%)	.65

THA, total hip arthroplasty; SD, standard deviation; ASA, American Society of Anesthesia; VAS, Visual Analog Scale; HHS, Harris Hip Score.
[a] ASA score was dichotomized (ASA = 1 and ASA 2, 3, 4 as ASA > 1 for statistical analysis).

In the same period, 469 patients (43 bilateral) received THA without any previous injection. Seventeen had one or more of the exclusion criteria, leaving 495 THAs (452 patients) available for assessment.

There were no differences in baseline characteristics between the 2 groups (Table 1).

The infection parameters in the preoperative blood samples, including C-reactive protein and erythrocyte sedimentation rate, showed no increased levels. None of the patients showed any clinical signs of infection pre-operatively which could affect the hip joint.

The identified risk factors for postoperative PJIs were comparable between both groups (Table 1).

Clinical Outcome

The mean follow-up was 51.9 months (±17.5). The clinical outcomes in terms of VAS pain scores (1.4 ± 2.2 vs 1.7 ± 2.1 points, $P = .11$), mHHSs (77 ± 17 vs 75 ± 16 points, $P = .09$), and HOOSs (79 ± 21 vs 76 ± 21 points, $P = .24$) did not differ between the injection group and the control group (Table 2).

Peroperative and Postoperative Complications

In the injection group, 30 of 118 hips (25.4%) had at least one complication after performing THA, whereas in the control group 71 of 495 patients (14.3%) had at least 1 complication ($P = .005$). The different types of complications are summarized in Table 3.

There was no difference in the incidence of most perioperative or postoperative complications between the injection and the control group (Table 3). However, we found a higher rate of PJIs and postoperative wound infections in the injection group compared with the control group (respectively $P < .001$ and $P = .01$). In the injection group, there were 5 PJIs compared with no PJIs in the control group. Two patients who developed a PJI received their injection within 3 months before THA, the other 3 patients received the IAHA injection between 3 and 6 months preoperatively. Only 1 patient had a risk factor (diabetes mellitus) for developing a PJI at the time of surgery.

Four out of 5 PJIs were detected within 1 year postoperatively. In all of these cases, aspiration fluid, tissue or swab culture (in the event of a surgical treatment) showed at least 2 positive cultures of the same organism. In 3 patients, an infection with coagulase-negative Staphylococcus was diagnosed, in 1 patient the combination of Peptostreptococcus species and coagulase-negative Staphylococcus, and in 1 patient *Staphylococcus aureus*.

Two PJIs were managed with a 2-stage revision arthroplasty. No reinfection occurred in these cases before the end of follow-up (10 months and 56 months respectively). One patient underwent a Girdlestone procedure with implantation of a cement spacer combined with antibiotics. Reimplantation of THA has not yet been performed due to elevated infection parameters (C-reactive protein and erythrocyte sedimentation rate) (30 months). The fourth patient refused to undergo a 2-stage revision arthroplasty of her infected THA. She remains under oral antibiotics since the time of diagnosis. The fifth patient reacted well to intravenously administered antibiotics (1 year postoperatively after having a wound infection direct postoperatively) and 6 years later the THA is still in situ without current use of antibiotics or signs of infection. The diagnosis of PJI was based on 2 separate aspirations of the arthroplasty. Although intravenous administration of antibiotics is not recommended as independent treatment option, this patient reacted well on this treatment.

All postoperative wound infections reacted well to antibiotics (oral and/or intravenous). No operation (eg, evacuating pus or secondary closure of the wound) was necessary.

Table 2
Clinical Outcome Measures.

Outcome Measure	Injection Group	Control Group	*P*-Value
VAS for pain, mean (SD)	1.4 ± 2.2	1.7 ± 2.1	.11
Modified HHS, mean (SD)	76.7 ± 16.5	74.6 ± 15.8	.09
HOOS, mean (SD)	78.5 ± 20.5	75.5 ± 21.2	.24

SD, standard deviation; VAS, Visual Analog Scale; HHS, Harris Hip Score; HOOS, Hip disability and Osteoarthritis Outcome Score.

Discussion

The most important finding of the present study was an increased infection rate (both PJI and wound infection requiring >1 week of antibiotics) after THA within 6 months of IAHA injection, compared to THA without prior IAHA injection. The total number of complications was significantly higher in the IAHA group, although the incidence of complications other than infection did not differ between both groups, and clinical outcome measures were comparable.

To our knowledge, PJI risk for THA after prior IAHA has never been reported. IAHA injection is considered a safe and well-tolerated procedure [23]. We did not observe deep infections or other major adverse effects in our own series of 839 intra-articular injections of the hip, although the present study was not designed to detect infection after IAHA. Yet, we observed a higher rate of PJIs

Table 3
Incidence of Peroperative and Postoperative Complications.

Complication	Injection Group (n = 118)	Control Group (n = 495)	*P*-Value
PJI of the THA	5/118 (4.2%)	0/495 (–)	**<.001**
Wound infection requiring >1 wk of antibiotics	10/118 (8.5%)	14/495 (2.8%)	**.01**
Trochanteric bursitis	9/118 (7.6%)	26/495 (5.3%)	.38
Wound leakage >1 wk	0/118 (–)	6/495 (1.2%)	.60
Accidental periprosthetic fractures	2/118 (1.7%)	6/495 (1.2%)	.65
Aseptic loosening of the stem	0/118 (–)	5/495 (1.0%)	.59
Tendinitis gluteus medius muscle	4/118 (3.4%)	5/495 (1.0%)	.08
Leg length difference >2 cm	1/118 (0.9%)	0/495 (–)	.19
Recurrent dislocations	0/118 (–)	2/495 (0.4%)	1.00
Peroperative greater trochanter fracture	2/118 (2.5%)	7/495 (1.4%)	.69
DVT	0/118 (–)	1/495 (0.2%)	1.00
Lung embolism	0/118 (–)	2/495 (0.4%)	1.00
Temporary sciatic nerve palsy	0/118 (–)	1/495 (0.2%)	1.00

DVT, deep venous thrombosis; THA, total hip arthroplasty; PJI, periprosthetic joint infection.
P <0.001 for the PJI of the THA, $P = 0.01$ for the wound infection.

and wound infections in the injection group compared with a parallel group of patients who were operated on without previous injections in the affected hip joint. The rate of PJIs in the study group (4.2%) was high compared with the rate found in the Norwegian Arthroplasty Register over a 21-year period, reporting 0.6% PJI cases (110,882 THAs) [24].

To date, controversy exists regarding possible increased infection risks when performing arthroplasty after previous intra-articular injections. A systematic review on intra-articular CS prior to THA identified 2 studies that reported higher infection risks for THA after intra-articular injection, and 7 studies that found no difference [7]. Of the 2 studies reporting increased infection rates, Kaspar et al [8] showed PJI rates of 10% (4/40 patients) in their CS group, compared to 0% in the control group (0/40 patients), but their study lacked statistical power. Second, Ravi et al [25] included 37,881 THA patients in their database study, of whom 2468 received an intra-articular injection within 5 years prior to THA (69% <1 year). Patients who had an injection within 1 year of THA showed higher PJI rates than patients who did not receive prior intra-articular injection (3.3% vs 2.4%, $P = .04$). Also, controlling for confounders, an elevated hazard ratio of 1.37 of PJI was found after prior injection [25]. Additionally, McIntosh et al found no difference in infection rate in a matched cohort of 448 (224 per group) THAs. Yet, for the 3 patients who developed deep PJI, mean time between injection and THA was 44 days (±23), compared to 112 days (±23) for the entire cohort, raising concern for increased deep infection risk after intra-articular CS injection within 6 weeks of THA [9]. More recently, Werner et al [26] showed that the incidence of infection after THA for patients who underwent previous intra-articular injection within 3 months was significantly higher at 3 months (odds ratio [OR] 1.9, $P = .004$) and 6 months (OR 1.5, $P = .019$) [26]. There was no significant difference in infection rates in patients who underwent THA between 3 and 6 months or 6 and 12 months after ipsilateral hip injection, compared to controls [26].

Comparable findings have been reported for total knee arthroplasty (TKA), with a systematic review (2014) showing 1 out of 4 available studies reporting an increased risk of PJI after prior CS injections [27]. However, more recently Richardson et al [6] performed a database study including 58,337 TKAs, including IAHA injections for the first time. Prior injection with either CS or IAHA ≤3 months of TKA was an independent risk factor for PJI, with ORs of 1.21 and 1.55 respectively. There was no increased PJI risk with injections >3 months prior to TKA. Based on these findings, several authors stated that intra-articular injections ≤3 months of TKA should be avoided [6,28]. Thus, the available evidence is a reason for caution regarding arthroplasty surgery after recent intra-articular injections.

Despite extensive assessment of the available data, we were not able to provide plausible explanations for the observed differences in outcome after previous HA injections. Levy et al [29] suggested that due to biofilm formation, indolent and culture-negative bacterial growth in osteoarticular tissues may be more common than previously recognized. In this context, it is interesting to note that, due to their hyaluronidase production, staphylococci and streptococci could use hyaluronan as an energy source and virulence factor [30,31]. Although it is in principle possible that IAHA injections and later postoperative hematomas after joint replacement might lead to activation of subclinical infections, the mechanism mediating the statistical association between IAHA injections and subsequent peri-implant infections remains unclear.

Our retrospective study design is a limitation. Also, as with previous studies on this topic, our relatively small sample is a limitation, given the overall low number of PJIs. However, our cohort study is by far the largest that reports on the effects and safety of intra-articular injections prior to THA, and the first ever to report on the effect of IAHA. Finally, while the use of IAHA for hip OA was relatively common when we performed our study, recent guidelines have recommended against the use of HA in hip OA, since existing data remain ambiguous as to whether IAHA in the hip joint shows any effect compared to placebo [32–34]. Consequently, the use of IAHA of the hip is expected to decline sharply in the coming years. Yet, our data do suggest that IAHA injections with close proximity to subsequent THA may present a risk of increased PJI rates, and thus THA should preferably be postponed. As such, our findings may still serve as further evidence of the increased risk of PJI after previous intra-articular injections. Additional research is necessary concerning the immunological action(s) of IAHA, and larger prospective series would provide us with more robust evidence regarding the risks of preoperatively intra-articular administered agents on the outcome of hip and knee arthroplasty.

Conclusion

In conclusion, our data suggest that patients receiving IAHA injections of the hip within 6 months to subsequent THA may be at risk for increased rates of PJI. Although prospective studies are needed to confirm our findings, we would presently recommend against performing THA within 6 months after IAHA administration.

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