Long-Term Intraocular Pressure Changes after Pars Plana Vitrectomy: An 8-Year Study

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Abstract

Purpose: To investigate the long-term changes of intraocular pressure (IOP) after pars plana vitrectomy (PPV).

Methods: This was a retrospective historical cohort study. Patients with a history of vitrectomy in one eye by a single surgeon were enrolled. IOP of the operated eye was compared to the fellow eye. Previous scleral buckling, IOP rise due to surgical/anatomic complications, silicone oil (SO) emulsification, and contralateral ocular hypertension/glaucoma at recruitment were exclusion criteria. "Significant IOP rise" (>6.0 mmHg) and development of open angle glaucoma (OAG) were the main outcome measures.

Results: Two hundred and twenty-five eyes were included. Mean and median follow-up duration were 20.6 and 9.0 months, respectively. Mean baseline IOP and mean final IOP were 13.53 ± 3.75 mmHg and 16.52 ± 6.95 mmHg, respectively (P < 0.001). Forty-three patients developed “significant IOP rise” with no statistically significant relation to the indication of vitrectomy, the postoperative lens status, and number of vitrectomies (P = 0.410, P = 0.900, and P = 0.160, respectively). SO injection raised the probability of IOP rise in the long-term (P = 0.028). OAG occurred in 17 patients (7.5%) with no association to SO tamponade (P = 0.840). “Significant IOP rise” and OAG occurred in 3 and 1 control eyes, respectively, significantly lower than the rates in study eyes (P < 0.001).

Conclusion: Mean IOP slightly rose in the long-term after PPV. SO tamponade was associated with IOP rise in the long-term but not with the incidence of OAG. Both IOP rise and OAG were more probable after vitrectomy.

Keywords: Intraocular pressure, Open angle glaucoma, Pars plana vitrectomy, Silicone oil

INTRODUCTION

Introduced in 1971 by Machemer et al., pars plana vitrectomy (PPV) is one of the most frequently performed procedures in ophthalmology today, and its indications and techniques are continuously expanding.1 Cataract formation and retinal detachment (RD) are among known long-term complications of vitrectomy. Other complications of vitrectomy such as acute intraocular pressure (IOP) rise due to silicone oil (SO) overfilling, intraocular gas expansion, and postoperative inflammation are well described in past studies.2-4 The development of chronic open angle glaucoma (OAG) has been postulated after vitrectomy. Chang and later, Luk et al. proposed exacerbation of oxidative stress in the anterior segment of the eye after lens removal during vitrectomy which can lead to OAG as a long-term complication of vitrectomy.5,6 They did not take into account the IOP rises which failed to meet the criteria of OAG. On the other hand, Chang’s study included eyes with previous vitrectomy or scleral buckling, traumatic lens dislocation, and retained lens fragments which...
have other factors predisposing the eye to IOP elevation. Some newer studies confirmed that the incidence of ocular hypertension (OHT) or OAG is higher after vitrectomy.7-10 By contrast, some other studies reported no increased risk of IOP rise or OAG in the long-term.11-14 Some of these studies limited the cases to idiopathic epiretinal membrane (ERM) ± macular hole (MH) to reach a more homogeneous study population.12,13 Other authorities such as Lalezary et al. and Yu et al. included diverse spectrum of vitrectomy indications.11,14 They all concluded in their series that vitreoretinal surgery even after lens removal does not seem to have a role in IOP rise in the long-term. The study population size, follow-up period, indication of PPV, and demographic characteristics of study cases is quite diverse in the above-mentioned studies. Therefore, it is not surprising that there would be no consensus about the increased risk of IOP rise or OAG in the long-term. The influence of repeated vitrectomies and the underlying disease on IOP rise and OAG after vitrectomy are still in debate.

In this study, we tried to find answers to these questions: Is PPV correlated with IOP rise in the long-term? And if so, do the underlying disease and repeated vitrectomies have any role in this process?

**METHODS**

This is a single surgeon retrospective cohort study. The protocol was approved by our local institutional review board and ethics committee. The study protocol adhered to the tenets of the Declaration of Helsinki. Medical records of patients who had undergone elective 20- and 23-gauge vitrectomy from March 2003 to October 2012 were reviewed. Demographic data, past medical history, drug history, and clinical examinations including anterior chamber angle depth (as determined by slit-lamp biomicroscopy, and in the eyes with shallow anterior chamber angle in slit-lamp examination, by gonioscopy), lens status, IOP (Goldmann applanation tonometer), optic nerve head cupping (as determined by biomicroscopy with 90 diopter non-contact lens), and the indication for vitrectomy including diabetic retinopathy (DR) (tractional RD, vitreous hemorrhage [VH] due to proliferative DR and tractional clinically significant macular edema), MH, ERM, RD, and VH due to diseases other than DR or RD were recorded. Details of the surgical procedure including SO injection, intravitreal bevacizumab injection, and concomitant lens removal were also documented. Patients undergoing repeated vitrectomies, either due to failed initial vitrectomy or a new indication, were also included in the study.

Patients with previous or concomitant scleral buckling surgery, or previous or subsequent vitrectomy of the fellow eye were excluded. Other exclusion criteria were: history of glaucoma, OHT (IOP >22.0 mmHg with normal cupping and normal visual fields), follow-up of <3 months, occurrence of postoperative endophthalmitis, trauma, use of medications with a potential for rising the IOP (especially corticosteroids), peripheral anterior synechia (PAS), iris neovascularization, and any optic nerve head abnormality which prevented correct estimation of cup-disc ratio. Eyes that developed postoperative complications which could raise the IOP, including posterior synechiae, PAS, angle neovascularization, VH in aphakic eyes, and occlusion of peripheral iridectomy in the presence of SO in aphakic eyes, were also excluded.

Antibiotic and steroid drops were used postoperatively and were tapered and discontinued during the first postoperative month. Change of IOP through the follow-up period was the main outcome measure. Due to the diurnal variation of IOP which is between 2 and 6 mmHg over 24 h,15 the second outcome measure was determined as >6.0 mmHg increase in IOP (significant IOP rise) for more than 1 month, and documented at least in two consecutive visits. Patients who needed SO removal due to IOP rise, or who underwent medical and/or surgical treatments for control of the IOP were also put in the same category of “significant IOP rise.” The term OAG was used for patients who showed progressive optic nerve head cupping (as determined by ophthalmoscopy and serial drawings) in the setting of an open angle in addition to the presence of IOP rise. The condition of the contralateral eye was also recorded and used as control.

Statistical analysis was performed using STATA software (version 11.1, Inc., StataCorp LLC, Texas, USA). Qualitative variables are presented as percentages, and quantitative data are expressed as mean values with standard deviations (SD). The patients were sorted in four separate settings based on: (1) intraoperative SO injection, (2) postoperative lens status, (3) number of vitrectomies, and (4) indication of surgery. The log-rank test was used to compare Kaplan–Meier survival curves for each of these groups. The significant level was assumed <0.05.

**RESULTS**

A total of 1023 patients had been treated by elective 20–23 G vitrectomy from 2003 to 2012, and among them, 225 eyes were enrolled based on the inclusion and exclusion criteria. Baseline characteristics of the patients and operative data of the study cohort are presented in Table 1.

The mean age of patients was 45.04 ± 17.67 years. Mean and median duration of follow-up were 20.6 and 9.0 months, respectively. Mean ± SD baseline IOP was 13.53 ± 3.75 mmHg in the study eyes and 13.60 ± 2.25 mmHg in the fellow eyes (P = 0.604) [Table 2]. Mean ± SD final IOP was 16.52 ± 6.95 mmHg and 14.12 ± 3.08 mmHg in the study eyes and the fellow eyes, respectively (P < 0.001). The distribution of IOP difference between baseline and the last visit is demonstrated in Figures 1 and 2.

There was a statistically significant difference between the baseline and final IOP of both the study (P < 0.001) and fellow eyes (P = 0.004) [Table 2].

“Significant IOP rise” occurred in 43 vitrectomized eyes (19%) compared to 3 fellow eyes (1%) which developed significant IOP rise through the follow-up period (P < 0.001, Figure 3).
OAG was observed in the fellow eye of only one patient compared to 17 vitrectomized eyes which developed OAG during the follow-up period \( P < 0.001 \), Figure 4.

One hundred and fifty-two eyes (68%) were phakic before operation, from which only 64 eyes (28%) remained so to the last follow-up visit [Table 1]. Kaplan–Meier analysis demonstrated the “Significant IOP rise” incidence as to be 33% and 32% at 8 years for non-phakic and phakic study eyes, respectively \( [P = 0.900, \text{ Figure 5}] \).

OAG was observed in the fellow eye of only one patient compared to 17 vitrectomized eyes which developed OAG during the follow-up period \( P < 0.001 \), Figure 4.

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The most common indications for vitrectomy were rhegmatogeneous RD (RRD) (116 patients) followed by DR (68 patients), MH and ERM (20 patients), and VH (15 patients).

The incidence of “Significant IOP rise” in study eyes at 8 years was not statistically different between the previously defined vitrectomy indications \( [P = 0.415; \text{ log-rank test}] \).
The number of vitrectomies in each eye did not seem to affect incidence of IOP rise. Log-rank test (Kaplan–Meier analysis) revealed no significant difference between patients who underwent just one vitrectomy and those with twice or more vitrectomies \( P = 0.165 \), Figure 6.

SO tamponade was performed for a total of 119 patients of the study population and 31 of them experienced significant IOP rise during the whole follow-up period. SO tamponade raised the chance of “significant IOP rise” in the long-term \( P = 0.028 \), Figure 7.

OAG was observed in 17 study eyes (7.5%). Unlike IOP rise, which showed relation to SO tamponade, there was no significant association between incidence of frank OAG and SO tamponade (log-rank test, \( P = 0.840 \)). There was no significant relation between incidence of OAG and number of vitrectomies lens status and indication of surgery (log-rank test, \( P = 0.490 \), \( P = 0.716 \) and \( P = 0.314 \), respectively).

**DISCUSSION**

The present study investigated the long-term changes in IOP after PPV over a relatively long follow-up course. Mean IOP rises significantly in vitrectomized eyes in the long-term. However, this IOP elevation is of relatively little clinical significance. We found “significant IOP rise” in 19% of the eyes which was not associated with the indication for PPV, the presence or absence of crystalline lens after surgery, or the number of surgeries. SO tamponade showed tendency to raise IOP significantly.

Results of the current study show that there was a statistically significant rise in IOP of both the study and fellow eyes during the study, but vitrectomized eyes ended with higher IOPs than the fellow eyes. We do not have a plausible explanation for the rise in the IOP of both groups with time, it may be due to the effect of aging on IOP, but the difference in IOP of the two groups at the end of the study can be attributed to the effect of vitrectomy, as the baseline IOPs were the same.
Large previous clinical trials have shown that IOP is the only risk factor of glaucoma that can be modified to halt the progression of optic nerve damage.\textsuperscript{15-17} Chang, and after him Luk et al. claimed that OAG may develop after vitrectomy as a long-term complication.\textsuperscript{16} Chang postulated the hypothesis that increasing oxygen tension in the anterior chamber angle following vitrectomy may cause oxidative stress in the trabecular meshwork and lead to OAG.\textsuperscript{5} Chang’s hypothesis was based on the results of the previous studies which had shown that there is a gradient of oxygen tension in the vitreous body from the retinal surface to the anterior vitreous, and also that there is a higher concentration and more uniform distribution of oxygen in the vitreous cavity after vitrectomy.\textsuperscript{18,19} He followed 68 vitrectomized eyes for a mean of 56.9 months (range, 7–192 months) and reported an incidence of 15–20% for development of OAG after vitrectomy. He showed that OAG took longer time to develop in phakic eyes than pseudophakic eyes because of the protective effect of crystalline lens against oxidative damage of trabecular meshwork. In his series, Chang included eyes with traumatic lens dislocation, retained lens fragments, and previous retinal surgery that may have a potential effect on IOP.\textsuperscript{5} Luk et al. reported an incidence of 7.9% for OAG by studying 101 vitrectomized eyes for 51 months (range, 6–80 months).\textsuperscript{6} They limited their cases to ERM and MH to have a more homogeneous study group and attributed their lower rate of OAG development to removing possible confounding factors of Chang’s study, for example, RD, trauma, and retained lens material. Luk’s results confirmed Chang’s by reporting a higher incidence of OAG in pseudophakic eyes compared to phakic eyes.\textsuperscript{6} Neither Chang nor Luk evaluated the full spectrum of post-vitrectomy IOP changes and just focused on OAG. Fujikawa et al. conducted a study with a similar patient population as Luk’s study.\textsuperscript{7} They enrolled 118 eyes undergoing PPV for ERM and MH and found a significantly higher chance of increased IOP in PPV eyes than un-operated eyes (\(P < 0.001\)) in the MH but not ERM group. Fujikawa suggested that the clogging of trabecular meshwork with intraoperative sludge after gas-fluid exchange and also face down position may explain the increased risk of IOP rise.\textsuperscript{7} They used non-contact tonometer to evaluate IOP that is not the gold standard for IOP measurement. Koreen et al. enrolled a large study population (285 eyes) with the broadest spectrum of inclusion criteria including previous scleral buckling and vitrectomy.\textsuperscript{8} They reported a high overall OAG incidence of 11.6%. There was a huge difference in OAG incidence between phakic and non-phakic eyes, 1.4% versus 15.0%.\textsuperscript{8} In a more recent series in 2014, Wu et al. chose the narrowest inclusion criteria among other related studies- 198 eyes with ERM - in order to minimize the variability in surgical procedure that may impact IOP, optic nerve, or nerve fibers.\textsuperscript{10} They reported a higher incidence of “sustained IOP elevation” in the PPV group compared to the un-operated group. Family history of OAG and pseudophakia were determined to be the risk factors of IOP elevation.\textsuperscript{10} Yu et al. had opposite results.\textsuperscript{14} They enrolled a large study population (441 eyes) covering a vast majority of PPV indications including MH, ERM, RD, choroidal neovascularization, synchysis scintillans, and vitreomacular traction syndrome. The incidence of OHT or OAG in the PPV group was not significantly higher than fellow eyes. In addition, postoperative phakic or pseudophakic status of the eye did not influence the incidence of OAG or OHT. Lalezary et al. analyzed IOP changes after vitrectomy in 101 eyes with various indications of PPV - including RD and DR complications - and reported an incidence of 7–13% for IOP rise (>4.0 mmHg from baseline) at 4 years, and 46% to 53% at 8 years of follow-up.\textsuperscript{11} They reported no cases of OAG requiring treatment. Diabetes, previous vitrectomy, and postoperative crystalline lens status did not increase the risk of IOP rise. In 2015, Mi et al. reported a retrospective series of 234 eyes that received PPV for ERM and MH.\textsuperscript{12} With a mean follow-up period of more than 4 years, they had 2.6% and 1.7% OAG incidence in the operated and non-operated eyes, respectively, which was not statistically significant (\(P = 0.750\)). In addition, they observed no mean IOP change in both the operated and non-operated groups. They suggested that indocyanine toxicity might explain the high rate of OAG in Luk’s et al. series (7.9%) since they had used indocyanine green dye in a majority of their patients.

In the only published prospective cohort till now, in 2014, Lalezary et al. evaluated IOP and peripapillary retinal nerve fiber layer (pRNFL) thickness changes after PPV for ERM, MH, or vitreous opacities.\textsuperscript{20} Of 40 enrolled patients, 38 completed the study. Evaluations included IOP, gonioscopy, cup/disc ratio (fundus photography) measurements, and macular and pRNFL optical tomography. All the evaluations were performed before surgery, 3 months, and 12 months after surgery. One year after vitrectomy, mean IOP in pseudophakic eyes increased from 14.5 ± 3.2 mmHg to 16.0 ± 2.8 mmHg (\(P = 0.041\)). In contrast, 10 phakic study eyes remained so at 1-year visit. Mean baseline IOP was 17.3 ± 4.7, and mean final IOP was 16.9 ± 2.2 (\(P = 0.61\)). In addition, a statistically significant decrease was observed in the inferior pRNFL at 1-year follow-up.Finally, a recently published study by Tognetto et al. concluded that uncomplicated PPV for ERM does not increase the risk of OHT or OAG.\textsuperscript{13} They enrolled 368 eyes that received PPV for ERM. The incidence of OHT was 5.7% in both the PPV group and the un-operated group, and OAG occurred in 1.4% of operated eyes.\textsuperscript{13} Our results are comparable to Lalezary’s study in case of IOP rise. With comparable duration of follow-up, the total percentage of patients with “significant IOP rise” (>6.0 mmHg) in the current study was 19% compared to 7–13% at 4 years in Lalezary’s study. However, they reported much higher percentage of significant IOP rise after 8 years’ follow-up (46–53%). Among other studies which defined a parameter as “sustained or significant IOP rise” or “ocular hypertension” – defined as IOP ≥22.0 mmHg or more than 4–5 mmHg increase from baseline, Mi et al., Fujikawa et al., and Tognetto et al. reported no statistically significant difference.
between the vitrectomy group and fellow eye group.\textsuperscript{7,12,11} Conversely, Wu \textit{et al.} reported a large difference between PPV eyes and fellow eyes (19.2\% vs. 4.5\%, respectively, \(P < 0.001\)).\textsuperscript{10}

We observed 17 cases (7.5\%) of OAG in the last follow-up visit. Chang reported 15–20\% incidence of OAG that is more than twice our result, and no other study has reported this high percentage of OAG. As previously mentioned, it may be due to including nearly all PPV indications in their study.\textsuperscript{2} Chang’s definition of OAG was as follows: glaucoma suspects, which were defined as eyes with more than 4 mmHg higher IOP than their fellow eyes; new onset glaucoma, which was defined as IOP >30 mmHg or high IOP + optic disc and/or visual field changes compatible with glaucoma; and preexisting glaucoma. Our definition of glaucoma was high IOP with the progression of cup/disc ratio. Similarly, Koreen \textit{et al.} who chose a large variety of PPV indications comparable to Chang’s study, reported a high incidence of 11.6\% for OAG.\textsuperscript{6} Luk limited the analysis to just MH and ERM cases.\textsuperscript{6} Their incidence of OAG was 7.9\%, nearly half of Chang’s study. Lalezary reported no cases of OAG.\textsuperscript{11} He hypothesized that Chang has enrolled all indications of vitrectomy, including RD, retained lens fragments, and dislocated intraocular lens which are at an increased risk of OAG. Therefore, the incidence of OAG was high in his study. Lalezary also claimed that Luk \textit{et al.} have focused on visual field defect for the diagnosis of glaucoma which will be affected by vitreectomy itself and indocyanine toxicity, so they may have overestimated the diagnosis of glaucoma. Unlike Lalezary and Luk, we did not limit our analysis to ERM and MH and included all cases undergoing PPV except for cases with previous retinal surgery and trauma, which may have IOP rise or develop glaucoma due to injury to the anterior chamber angle. However, just like Lalezary, we did not rely on visual field assessment for defining OAG because visual field defects can be caused by the retinal diseases for which vitreectomy was performed or by previous retinal treatments. The incidence of OAG in our study is close to Luk’s study (7.5\% vs. 7.9\%, respectively).

The elevation of IOP due to SO is a well-known early postoperative complication of PPV. In a recent study, Jabbour \textit{et al.} showed that more than 90\% of IOP elevations in PPV + SO tamponade occur within 6 weeks from surgery.\textsuperscript{23} In the long-term, glaucoma is the most common complication of SO emulsification.\textsuperscript{22} By excluding eyes with less than 3 months follow-up, SO emulsification, and any other early complications related to SO tamponade, we tried to reduce the known confounding effects of SO tamponade to find possible effects of SO on the trabecular meshwork. We found a significantly higher incidence of “IOP rise” in eyes receiving PPV + SO tamponade (\(P = 0.030\)). We could not find any association between PPV + SO tamponade and OAG. Recently, Liu \textit{et al.} found a significant increase in the expression of inflammatory mediators including interleukin-6, interleukin-17, and tumor necrosis factor \(\alpha\) in the anterior chamber at the time of SO removal.\textsuperscript{23} This new information suggests an inflammatory state in the anterior chamber of eyes containing SO which in turn put the trabecular meshwork under an inflammatory stress.

The status of the lens (phakic vs. nonphakic) has been investigated in a number of previous studies. We observed that postoperative lens status did not make any difference in “significant IOP rise” or in the development of OAG. Chang hypothesized that the removal of the crystalline lens puts trabecular meshwork under increased oxidative stress after vitrectomy.\textsuperscript{5} He reported higher incidence and earlier occurrence of OAG after PPV in non-phakic eyes than phakic eyes. After that report, studies have had conflicting results. Koreen \textit{et al.} and Wu \textit{et al.} reported more prevalent OAG in non-phakic eyes.\textsuperscript{3,10} Conversely, Fujikawa \textit{et al.}, Mi \textit{et al.}, Lalezari \textit{et al.}, and Tognetto \textit{et al.} could not find a relationship between lens status and OAG after vitrectomy.\textsuperscript{7,11-13} Our results are in line with the second group.

In the current study, none of the indications of PPV, even RRD, which more commonly includes SO tamponade, made a statistically significant difference in the final IOP among the other indications. Yamamoto \textit{et al.} in a retrospective study in 2016 investigated long-term IOP changes after PPV in patients with RRD, ERM, and MH.\textsuperscript{24} They reported that in the long-term, IOP increased significantly in the RRD group but not in the ERM and MH groups. They did not use SO tamponade in their patients. They could not explain why the risk of IOP elevation was higher in the RRD group, but suggested pathophysiology of RRD and the procedures to treat a RRD to be the responsible cause. Interestingly, in their study, the rate of crystalline lens extraction was significantly lower in the RRD group compared to the ERM and MH groups.

There are original studies and even meta-analyses that suggest the correlation between diabetes mellitus and glaucoma.\textsuperscript{25,26} These studies explain common mechanisms that contribute to the development of glaucoma and DR. For example, Toda \textit{et al.} investigated the important role of nitric oxide (NO) in regulation of ocular hemodynamics and cell viability.\textsuperscript{27} They showed that impairment of NO synthesis due to dysfunction of vascular endothelial cells in diabetes would affect retinal and optic nerve blood circulation as well as inducing oxidative stress to retinal cells and trabecular meshwork. However, we could not find a significant correlation between DR complications, as indications for PPV, with incidence of glaucoma. Mean baseline IOP in this group changed from 14.26 ± 3.45 mmHg to 17.69 ± 6.65 mmHg at the last visit in the operated eyes (\(P = 0.001\)). In the fellow eyes, it changed from 14.19 ± 2.08 mmHg at baseline to 14.46 ± 3.23 mmHg at the last visit (\(P = 0.389\)). A possible explanation could be that a longer follow-up period may be needed for diabetes-mediated mechanisms to bring the aqueous outflow damage to a significant level. In addition, as a limitation of our study, we did not check the diabetic control status of the patients, which can be a major factor in determining when cellular and microvascular dysfunctions may occur.

To the best of our knowledge, the influence of the number of vitrectomies has been investigated in few previous studies.
Our results showed that the number of vitrectomies does not have an effect on IOP in the long-term.

The study has limitations inherent to every retrospective study, so its results should be interpreted with caution, but the relatively large sample size makes it reliable. Results of the current study may not be applicable to other studies with different demographic data and indications of vitrectomy. In addition, the follow-up period and follow-up visit intervals were not the same for all patients.

We did not confirm the status of the anterior chamber angle of all eyes with gonioscopy, but just the eyes with shallow anterior chamber in slit-lamp examination. Therefore, it is possible that we have enrolled a number of eyes with a closed angle component. The next limitation of our study was that we did not take into account the kind of the SO used for our patients. We use 1300 cSt and 5700 cSt SO in our routine practice. However, since we excluded patients with SO emulsification, closed PI in aphakic eyes and closed angle eyes, we can expect that the viscosity of SO did not affect our results significantly. Another possible limitation of this study is that we did not exclude patients with diabetes that have been shown to be at a higher risk for glaucoma incidence. We used Goldmann applanation tonometer, which is the gold standard for measurement of IOP, while most of the previous studies used other IOP measuring devices, such as non-contact tonometers or tonopen. Although these devices are approved for IOP measurement, subtle differences from Goldmann tonometer may affect the statistical calculations.

In summary, mean IOP slightly rises in the long-term after PPV, and both “significant IOP rise” and OAG are more probable after vitrectomy. Among different variables in our study including the indication of surgery, number of vitrectomies, postoperative lens status, and SO tamponade, only the last one showed an association with a significant rise in IOP, and none were associated with the development of OAG, which occurred in 7.5% of the study eyes.

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Conflicts of interest
There are no conflicts of interest.

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