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Analgesic Efficacy of Pre-Operative Oral Pregabalin in Dacryocystorhinostomy Surgery

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ABSTRACT

Background: External dacryocystorhinostomy (DCR) is still considered the golden standard for lacrimal surgery. It is a painful procedure that involves intra- and extra-ocular dissection with a high prevalence post-operative nausea and vomiting (PONV).

Aims: This study was designed to evaluate the effects of preoperative oral pregabalin on postoperative pain and analgesic requirements in patients undergoing DCR surgery.

Design: A prospective randomized double-blind clinical trial.

Patients and methods: 100 American Society of Anesthesiologists (ASA) physical classes I and II patients in an age ranging from 18 to 65 years of either sex, had DCR surgery. Patients were divided randomly into two equal groups (each = 50). In pregabalin group, they received two capsules of pregabalin (one at the night of the surgery, the other at 2 hours before the surgery), while patients in control group received two identical placebo capsules. Hemodynamics were monitored, postoperative VAS scores, the time of first analgesic request, total pethidine requirements, and the incidence of PONV were recorded as well.

Statistical analysis: A prospective analysis of the collected data was performed using the SPSS program for Windows (version 22).

Results: The pregabalin group exhibited a significant lower incidence of postoperative pain, pethidine consumption and nausea, without any statistically significant differences regarding hemodynamic parameters in comparison to control group.

Conclusion: Preoperative oral administration of pregabalin can be a promising modality for alleviation of postoperative pain and reduction in postoperative opioid consumption.

KEYWORDS: Pregabalin, Analgesia, Dacryocystorhinostomy.

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INTRODUCTION

External dacryocystorhinostomy (DCR) is still considered the golden standard for lacrimal surgery. It is a bypass technique which creates an anastomosis between the lacrimal sac and the nasal mucosa through a bony ostium via an external skin incision. External DCR can be completed under either local or general anesthesia. ***[1]***

It is a painful surgical procedure that involves intra- and extra-ocular dissection, with a high prevalence post-operative nausea and vomiting (PONV). So, it is necessary to ensure a stress-free peri-operative period with adequate pain relief and a low incidence of PONV after DCR surgery. ***[2]***

Pre-emptive analgesia is a concept that may protect the central nervous system from harmful effects of noxious stimulus and the patient from the subsequent hyperalgesia as well as allodynia. It can be applied by administration of analgesic medications prior to surgical stimulation. ***[3]*** Various drugs such as local anesthetics, opioids, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, gabapentin, pregabalin, clonidine and dexmedetomidine have been used as preemptive analgesics. ***[4]***

Opioids are still the backbone of perioperative pain treatment. While their cautious usage provides analgesia via central and peripheral mechanisms, they are associated with a lot of consequences such as PONV, sedation, drowsiness, and itching, delaying discharge and increased charge of postoperative care. ***[5]***

Pregabalin is a lipophilic gamma-amino-butyric acid (GABA) analogue that binds to the voltage-gated calcium channels. It reduces the excitability of the dorsal horn neurons after tissue damage. ***[6]*** It has anticonvulsant, anxiolytic and sleep-modulating properties. It was shown to be effective in several models of neuropathic pain, incisional injury, and inflammatory injury. ***[7]***

Preoperative administration of pregabalin is supposed to be a promising technique of enhancing postoperative pain control and reduction in postoperative opioid consumption. ***[8]***

This study aimed to evaluate the effects of preoperative oral pregabalin on postoperative pain and analgesic requirements in patients undergoing DCR surgery. The primary outcome was to compare pain scores by visual analogue scale (VAS). Secondary outcomes were the time of first analgesic request, the total analgesic requirements during the postoperative 24 hours, the incidence of PONV, in addition to effect on hemodynamic parameters between the two groups.

PATIENTS AND METHODS

This study is a prospective randomized double-blind clinical trial included 100 ASA I and II patients of both sex with age between 18 and 65 years old. They were planned for elective DCR surgery under general anesthesia in Mansoura University ophthalmology center from January to December 2020. After approval by Institutional Board Review and Clinical Trial Registry, informed written consents were obtained from all subjects in the study after ensuring confidentiality. Exclusion criteria were mental, psychological or neurological disorders, patients with history of drug or alcohol abuse, history of know sensitivity to the used drugs, bleeding or coagulation diathesis, obese patients (body mass index (BMI) > 35), pregnancy and lactation, patients who refused to participate in the study.

Basic demographic characters including age, sex, ASA and BMI were recorded. All patients were subjected to preoperative history taking, clinical examination and laboratory investigations (complete blood count, coagulation profile, blood sugar, liver and renal function tests), in addition to ECG and ECHO when needed. Details of the anesthetic technique and the study protocol were clarified to the entire involved cases.

Eligible 100 patients were assigned randomly to two equal groups (n=50 in each group) using a computer-generated randomization schedule:

- Group C (Control) (n=50): patients received two identical placebo capsules.
- Group P (Pregabalin) (n=50): patients received two capsules of pregabalin (Lyrica 150 mg capsule, Pfizer, Freiburg, German);
  One at the night of the surgery, and the other at 2 hours before the surgery.

To achieve blinding, similar looking placebo capsules were arranged for the control group. Also, the recordings of all variables were collected by an investigator who was blinded to the group to which each patient was assigned.

Patients were kept fasting for eight hours prior to surgery. Two hours before surgery, patients received the appropriate capsule with 20 mL of water, according to the assigned group. Upon arrival to the operating room, basic monitors were applied (ECG, pulse oximetry, non-invasive BP), and baseline values were recorded.

An i.v. access was established and patients were premedicated with i.v. midazolam (0.05 mg/kg). After pre-oxygenation for 3 min at a rate of 6 L/min, anesthesia was induced with fentanyl (1 μg/kg) and propofol (2 mg/kg). Endotracheal intubation was facilitated by atracurium (0.5 mg/kg) and ventilation was controlled to maintain an end-tidal CO_2 of 30-35 mmHg. Thereafter; anesthesia was maintained with isoflurane (1-1.5%) in 40% oxygen and top up doses of atracurium (20% of intubating dose). Intra-operatively, all patients were administered i.v. normal saline (10 mL/kg/h).

By the end of the operation, the sevoflurane was turned off and residual muscle relaxation was reversed with neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg). Extubation was performed after return of sufficient spontaneous breathing and fulfilling its criteria, then oxygen was administered via a face mask. Later patients were transferred to the post anesthesia care unit (PACU) where they were monitored for two hours, then discharged to the ward to be observed for 24 hours post-operatively.

Collected data:

Heart rate (HR) and mean arterial blood pressure (MAP) were recorded before the procedure, after intubation, at 5-min intervals throughout the procedure, after extubation, and upon arrival to PACU, then every 30 min for 2 h until discharge from PACU.

Pain was assessed using VAS scale from 0 to 10 (0 representing no pain and 10 is the worst intolerable pain) on arrival to PACU, one, two, four, six, 12, 24 hours after surgery. Pethidine i.v. in a dose (1mg/kg) was administered if the score is ≥ 4 or upon request of the patient. The time to first analgesic request and total paracetamol requirements of the first 24 postoperative hours were recorded as well.

Incidence of PONV was reported during the first two hours in the PACU and subsequently in the ward for 24 hours. Vomiting or persistent nausea were managed by i.v. ondansetron (4 mg); total antiemetic requirements were also recorded.

Statistical analysis:

For calculation of the study sample size, we used a Priori G-power analysis (program version 3, Erdfelder E, Lang AG 2007, Universitat Dusseldorf) based on a previous study ***[9]***, with α (type I error) = 0.05 and β (type II error) = 0.2 (power = 80%). 47 patients per group was sufficient to find a difference of 25% in pain scores between them. A predicted 5% dropout of cases, so 50 subjects were required in each group to detect such difference.

Analysis of the collected data was performed using the SPSS program for Windows (version 22). At first, data normality was checked using Kolmogorov-Smirnov test. Qualitative or categorical variables were presented as numbers and percent to be compared using Chi-square test or Fisher exact test. Continuous variables were expressed as mean ± standard deviation if normally distributed, and median (range) for non-normal data. Both groups were compared parametrically using Student *t*-test, and non-parametrically with Mann-Whitney U-test. All data were considered statistically significant if P value ≤ 0.05.

RESULTS

In this study, 125 patients were assessed for eligibility; 25 patients were excluded, 100 patients were included, randomized and allocated either to control group (C) (50 patients) or to pregabalin group (P) (50 patients) as shown in flow chart. **(Figure 1)**

There was insignificant statistical difference between patients of both groups regarding age, sex, BMI, ASA physical status and duration of surgery (P > 0.05). **(Table 1)**

According to hemodynamics, both groups were comparable in HR and MAP throughout the surgery and during stay in PACU (P > 0.05). **(Figures 2 & 3)**

Considering pain scores measured by VAS, statistically significant low values were detected in pregabalin group relative to control group immediately on arrival to PACU, throughout PACU stay, up to 24h post operatively (P < 0.05). **(Table 2)** The time to the first request of analgesia was statistically significant longer in Group P when compared to Group C with (P value <0.001). Also, total postoperative pethidine consumption in the first 24h was significantly lower in Group P as compared to Group C. (**Table 3)**

Number of patients with nausea was statistically significant lower in Group P as compared to Group C (P = 0.046), without any other significance in number of patients with vomiting or total antiemetic dose of ondansetron between the two groups (P > 0.05).

(**Table 4)**

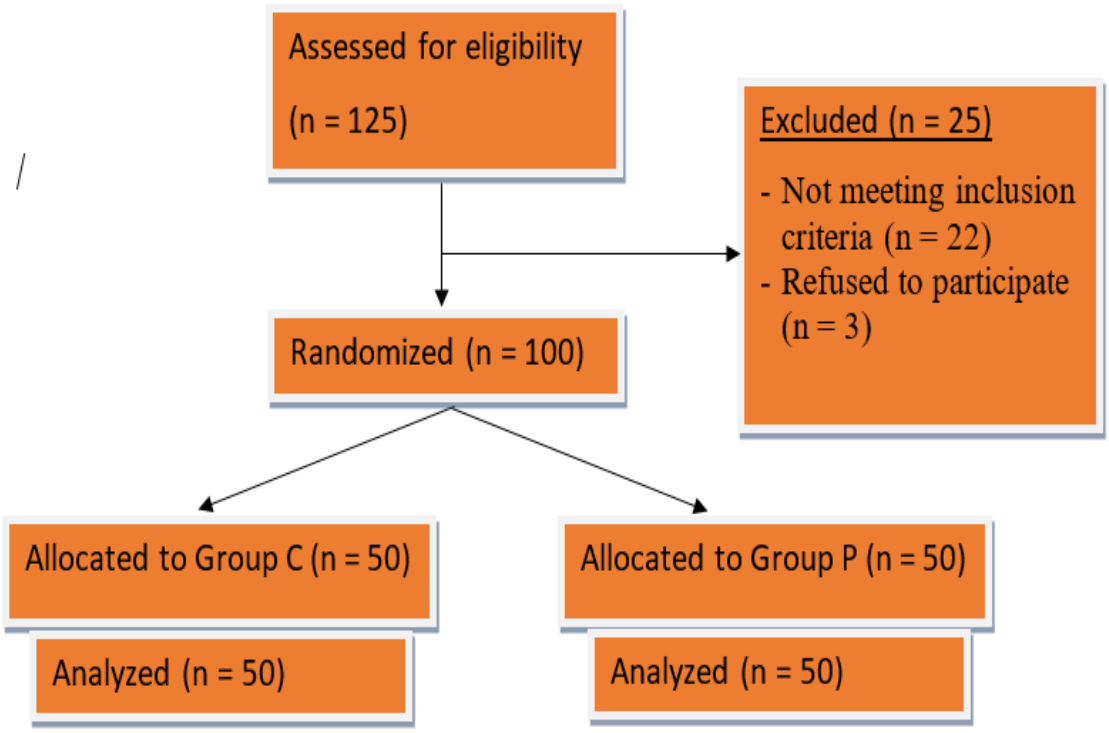

Figure 1. CONSORT flow chart

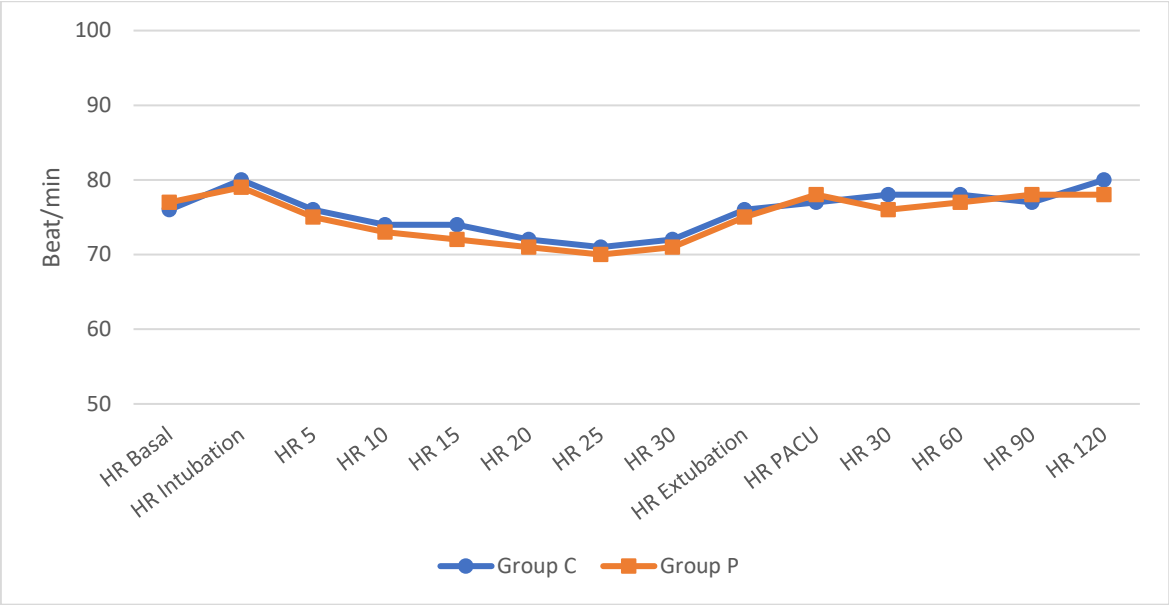

Figure 2. Intraoperative heart rate (HR) mean values (beat/min)

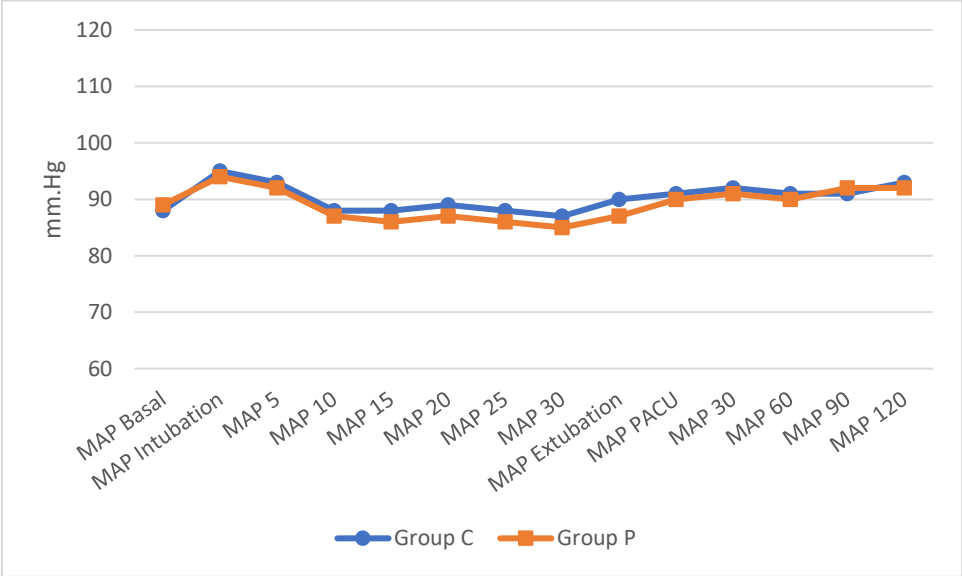

Figure 3. Intraoperative mean arterial blood pressure (MAP) mean values (mmHg)

Table 1. Demographic data:

		Control Group (C) (n. = 50)	Pregabalin Group (P) (n. = 50)	P value
Age (years)		47.16±14.33	43.58±12.18	**0.18**
BMI (kg/m²)		28.40±5.44	30.03±5.67	**0.14**
ASA	**I**	29(58.0%)	33(66.0%)	**0.41**
	II	21(17.9%)	17(34.0%)	
Sex	**Male**	26(42.0%)	20(40.0%)	**0.22**
	Female	24(48.0%)	30(60.0%)	
Duration of surgery (min)		35.20±11.77	31.60±12.32	**0.86**

ASA: American Society of Anesthesiologists, BMI: Body Mass index

Table 2. Postoperative VAS scores:

Time	Control Group (C) (n. = 50)	Pregabalin Group (P) (n. = 50)	P value
On PACU arrival	4(3-5)	3(2-4)	**0.001 ***
1h	4(4-5)	3(3-4)	**0.001 ***
2h	4(4-5)	4(2-4)	**0.025 ***
4h	4(3-5)	3(3-4)	**0.009 ***
6h	4(3-5)	4(2-4)	**0.004 ***
12h	3(2-4)	2(1-3)	**0.001 ***
24 h	2(2-3)	2(1-2)	**0.003 ***

Data were expressed as median and range.
VAS: Visual analogue scale.
* Significant P value < 0.05.

Table 3. First request of analgesia (min) and total post-operative pethidine consumption (mg):

	Control Group (C) (n. = 50)	Pregabalin Group (P) (n. = 50)	P value
First request of analgesia (min)	43.16±16.59	68.40 ± 30.17	**< 0.001 ***
Total pethidine consumption (mg)	180.00 ± 46.29	100.00 ± 37.03	**< 0.001 ***

Data were expressed as mean ± standard deviation.
* Significant P value < 0.05.

Table 4. Incidence of PONV and total antiemetic dose (mg) in the studied groups:

	Control Group (C) (n. = 50)	Pregabalin Group (P) (n. = 50)	P value
Number of patients with Nausea	14(28.0%)	6(12.0%)	**0.046 ***
Number of patients with Vomiting	8(16.0%)	4(8.0%)	0.36
Total antiemetic requirements (mg)	6.90±1.86	5.60±2.19	0.24

Data were expressed as mean ±standard deviation or number (percentage).
PONV: Postoperative nausea and vomiting.
* Significant P value < 0.05.

DISCUSSION

Post-operative pain is naturally sensed by nociceptive receptors. The operative trauma could induce hyperalgesia with subsequent prolongation of pain. On contrary to traditional analgesics with nociceptive nature, gabapentoids (gabapentin and pregabalin) reduce the activation of posterior horn neurons induced by tissue damage prior to afferent entry from their spots. Likewise, gabapentoids (given prior to surgeries) are suggested to reduce acute surgical pain. ***[10]*** Recently, pregabalin is utilized as an adjuvant medication in dealing with post-operative pain. A lot of researches are conducted to assess the efficiency as well as complications of

pregabalin in terms of pain management, however the outcomes are conflicting. Owing to changes in dosages, administration, and additional innate changes among various surgeries, generalization of the outcomes could not be done. ***[11]***

This study included 100 patients who were scheduled for elective DCR surgery under general surgery to evaluate the effects of preoperative oral pregabalin on postoperative pain and analgesic requirements.

In the current study, no statistically significant difference was detected between both groups regarding hemodynamics (HR and MAP) changes. These findings were in contrast to Agarwal report in cholecystectomy cases. ***[12]*** This can be explained by the difference in the nature of the surgical intervention in the two studies and the latter being a major surgery.

In the present study, pain score measured by VAS score showed statistically significant differences immediately on arrival to PACU, throughout PACU stay, up to 24h post operatively between the two studied groups. It was statistically significantly lower in pregabalin group.

In accordance to our results, Lam et al. conducted a meta-analysis in 2015 aiming to evaluate the postoperative analgesic efficiency as well as adverse outcomes following pregabalin administration under various surgical situations by utilizing an overall of 57 researches with 2033 cases taking pregabalin and 2033 control cases. In addition, they classified them in two subgroups as regards whether a single or several dosages (initiating from the night or days before surgeries) were given. In general, pregabalin has decreased postoperative pain scores for 24 hours irrespective of the dosage. However, there was no significant change in postoperative pain scores in such two subgroups. ***[13]***

In the same way, Alimian et al. assessed patients for DCR who were randomly allocated to pregabalin and control groups. They administered a single dose of pregabalin in the morning of surgery reporting that the pain intensity in pregabalin group after recovery, 30 min, 2h, 4h, 12h and 24h after the operation was significantly lower than that of control group (5.1 ± 1.5) (P = 0.001). ***[11]***

In another trial done by Agrawal and his colleagues, they reported that administration of pregabalin 150 mg 60 minutes prior to the surgery has markedly reduced pain degree as compared to the controls in patients undergoing laparoscopic cholecystectomy ***[12]***

Parallelly, Hill and his colleagues assessed the efficiency of administration of 50 mg and 300 mg pregabalin following dental surgeries. They demonstrated that administration of 300 mg of pregabalin could markedly decrease the post-operative pain while the complications in such group exceeded that of controls and 50mg pregabalin. ***[14]***

In the current study, the time to the first request for analgesia was significantly longer in pregabalin group (68.40 ± 30.17 min) when compared to placebo group (43.16 ± 6.59 min) with (P value < 0.001). Total postoperative pethidine consumption in the first 24h was significantly higher in placebo group (180.00 ± 46.29) mg when compared to pregabalin group (100.00 ± 37.03) mg with (P value < 0.001). In harmony with these findings, it has been stated that the inclusion of preoperative oral pregabalin administration was accompanied with a marked decrease in morphine consumption all over postoperative 24 hours as compared to control groups. ***[15]***

Consistently, forty-six studies in another meta-analysis with an overall of 1610 cases taking pregabalin and 1636 control cases, revealed that pregabalin decreased total morphine consumption at 24 hours after the operation. ***[13]***

In agreement to current results, Alimian et al. found that only 7 cases required opioids as rescue analgesia in pregabalin group while they were 21 in the control group (P < 0.05). The possibility of drug administration in the controls was five times that of pregabalin group in patients undergoing DCR surgery. ***[11]***

On the other hand, Jokela and his colleagues evaluated different dosages of pregabalin (150, 300 and 600 mg) in major gynecological and laparoscopic surgery. No significant difference was detected among the three groups as regards to the times for the first rescue of fentanyl, its total dose, and the number of patients requiring acetaminophen with codeine. ***[16] [17]***

Similarly, Zhang and his colleagues documented in their systematic review that administration of pregabalin in dosages below 300 mg prior to the surgery cannot markedly reduce the pain in the postoperative period whereas increasing the dose could markedly alleviate the pain intensity, but increase the adverse effects of pregabalin. ***[18]***

Indeed, our series demonstrated that administration of 300 mg of oral pregabalin, one at the night of surgery, and the other at 2 hours before the surgery, has successfully decreased pain scores without adverse effects. However, this depends mainly on the type of surgery as 300 mg of pregabalin in divided doses can perform its full action without complications than one dose or dosages below 300 mg, but in minor and moderate procedures.

Our current results showed that there were 14 cases (28.0%) suffered from nausea and 8 cases (16.0%) with vomiting (only one attack) with total antiemetic dose of (6.90 ± 1.86 mg ondansetron) in control group while only six cases (12.0%) suffered from nausea and four cases (8.0%) of vomiting (only one attack) with total antiemetic dose of (5.60 ± 2.19 mg ondansetron) in pregabalin group with (P = 0.046, 0.36 and 0.24 respectively).

In terms of PONV, the results of a meta-analysis done by Grant and his colleagues in 2016 have supported the administration of preoperative pregabalin for PONV prevention as well as pain management. To the recent multidisciplinary protocols that involve non-opioid alternatives to achieve multimodal analgesia, pregabalin could be a great addition due to its effect on several comorbid endpoints occurring with general anaesthesia. ***[15]***

Parallel to our results, Alimian et al. showed that incidence of vomiting in pregabalin group was 2.5% (single case) and in the controls was 12.5% (5 cases) (P = 0.09) in patients undergoing DCR surgery. ***[11]***

CONCLUSION

Preoperative oral administration of pregabalin can be a promising modality for alleviation of postoperative pain and reduction in postoperative opioid consumption in patients undergoing DCR surgery.

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