Ascorbic acid versus magnesium for the prevention of atrial fibrillation after coronary artery bypass grafting surgery

Abdelhay Ebade[a], Walid S.Taha[a], Riham H.Saleh[a], Ashraf Fawzy[b]

Departments of [a]Anesthesia, [b]Cardiothoracic Surgery, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence to Abdelhay Ebade, MD, 1 Elmekawleen Elarab St. from Gesr Elsewase, Elnozha, Masr Elgidida Flat No. 5, Cairo 1135, Egypt
Tel: +20 100 441 2369;
fax: 002 0223641687
e-mail: ebade467@yahoo.com

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Objective

The aim of the study was to evaluate the prophylactic use of ascorbic acid or magnesium on frequency of postoperative atrial fibrillation (POAF) in patients undergoing coronary artery bypass grafting surgery with cardiopulmonary bypass.

Patients and methods

The study included 60 patients divided into three equal groups ($n = 20$): the control group (group C) received saline infusion, the magnesium group (group M) received 2 g magnesium sulfate after induction of anesthesia, 1 g after 12 h followed by 1 g/8 h daily until the fifth postoperative (PO) day and the ascorbic acid group (group A) received 2 g ascorbic acid after induction of anesthesia, then 1 g after 12 h followed by 1 g/8 h daily until the fifth PO day. Operative and PO data were recorded. Primary endpoint was detection of an episode of atrial fibrillation (AF) lasting more than 10 min or the requirement for urgent intervention due to AF.

Results

Sixteen (26.7%) patients developed POAF, eight (40%) patients in group C, five (25%) in group M, and three (15%) in group A, with significantly higher frequency in group C compared with group M ($P_1 = 0.041$) and group A ($P_2 = 0.001$) but with nonsignificantly ($P_3 = 0.083$) higher frequency in group M compared with group A. Four patients developed POAF on the first and 12 patients on the second PO day with nonsignificant intergroup difference. The mean duration of ICU stay was significantly longer in group C compared with groups M ($P_1 = 0.016$) and A ($P_2 = 0.006$), with nonsignificantly ($P_3 = 0.480$) longer duration in group M compared with group A. The mean duration of PO hospital stay was significantly longer in group C compared with groups M ($P_1 = 0.008$) and A ($P_2 = 0.004$), with nonsignificantly ($P_3 = 0.415$) longer duration in group M compared with group A.

Conclusion

Prophylactic use of ascorbic acid or magnesium significantly reduced the frequency of POAF after coronary artery bypass grafting surgery and significantly reduced ICU and hospital stay.

Keywords:
ascorbic acid, magnesium, postoperative atrial fibrillation, prophylaxis

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Introduction

Atrial fibrillation (AF) is still considered the most common arrhythmia occurring after cardiac surgery. It generally occurs between 24 and 96 h postoperatively, with a peak incidence on the second postoperative (PO) day. AF occurs in ~28–33% of the patients undergoing coronary artery bypass grafting (CABG) and in 30–63% of those operated for coexisting ischemic heart and valve disease. AF is often temporary and disappears after the recovery of mechanical and metabolic functions [1–3].

Multiple studies tried to explore the pathogenic mechanism underlying the development of postoperative atrial fibrillation (POAF). Oxidative stress has been strongly involved in the underlying mechanism of AF, particularly in the arrhythmia occurring in patients undergoing cardiac surgery with extracorporeal circulation. The ischemia/reperfusion injury occurring in the myocardial tissue contributes to the development of tissue remodeling, thought to be responsible for the functional heart impairment. Consequently, structural changes due to the cardiac tissue biomolecules attack by reactive oxygen species (ROS) and/or nitrogen species could account for functional changes in ion channels, transporters, membrane conductance, cytosolic transduction signals, and other events, all associated with the occurrence of arrhythmic consequences [4].

Current evidence suggest inhibition of prominent cardiac sources of ROS, such as nicotinamide adenine dinucleotide phosphate oxidase, and targeting subcellular compartments with the highest levels of ROS may prove to be effective therapies for AF.

Another proposed mechanism for AF is that multiple reentrant circuits develop within the atria, causing rapid depolarization of the surrounding atrial tissue. Magnesium regulates cellular enzymatic and metabolic processes throughout the body. In myocardial cells, magnesium antagonizes calcium and potassium channels. In addition, electrophysiologic studies have demonstrated slowed cardiac conduction and increased cardiac refractoriness with administration of magnesium.

These actions suggest that magnesium may inhibit substrate formation and the development of reentrant circuits within the atria that are responsible for the development and propagation of AF. Magnesium has an accepted role in the management of ventricular arrhythmias; however, the role of magnesium in the treatment and prevention of atrial tachyarrhythmias is less well defined [5,6].

Thus, the current prospective comparative study was designed to evaluate the therapeutic yield of the prophylactic use of ascorbic acid or magnesium on the frequency of POAF in patients undergoing CABG surgery.

Patients and methods

After approval of the study protocol by the local ethics committee and obtaining informed patient's consent, the current study was conducted between July 2010 and December 2013. Sixty patients assigned for elective CABG surgery with cardiopulmonary bypass (CPB) were enrolled in the study.

Patients with renal or hepatic dysfunction, patients with known hypersensitivity to the studied drugs, patients with chronic obstructive pulmonary disease, patients who had preoperative AF, permanent or temporary pacemaker, patients on medication with class I and III antiarrhythmic agents or digoxin, and patients with any degree of atrioventricular block were excluded from the study.

Patients were divided into three equal groups (n = 20): the control group (group C) receiving saline infusion, the magnesium group (group M), and the ascorbic acid group (group A). Group M received 2 g magnesium sulfate after induction of anesthesia, then 1 g after 12 h followed by 1 g every 8 h daily until the fifth PO day. Group A received 2 g ascorbic acid after induction of anesthesia, then 1 g after 12 h followed by 1 g every 8 h daily until the fifth PO day.

Patients were premedicated with midazolam at a dose of 0.03–0.05 mg/kg on arrival to the operating room. Arterial cannula was inserted in the radial artery by local anesthesia; monitors were attached then anesthesia was induced by propofol 1–2 mg/kg and cisatracurium 0.15 mg/kg with fentanyl 3–5 μg/kg, followed by controlled mechanical ventilation to keep $PaCO_2$ between 35 and 45 mmHg. Anesthesia was maintained by sevoflurane, cisatracurium 2 μg/kg/min, and fentanyl boluses when needed.

Heparin sulfate was given at a dose of 4 mg/kg and supplemented as needed to keep the activated clotting time longer than 400 s before going on CPB. Anesthesia was maintained on CPB by propofol 3–4 mg/kg/h and systemic temperature was allowed to drift to 34°C. Blood cardioplegia was prepared from equal volumes of normal saline and blood (1 : 1) and was composed of potassium chloride 30 mEq/l, sodium bicarbonate 26 mEq/l, and lidocaine 120 mg/l. Cardioplegia was given initially at a dose of 10–15 ml/kg followed by 5 ml/kg every 20–30 min. When inotropic support was needed, dobutamine 3–5 μg/kg/min was used.

Intraoperative hemodynamic data including heart rate, systolic and diastolic blood pressure, and central venous pressure changes were determined at time of induction of anesthesia, after CPB weaning, and 2 h thereafter. The number of grafted vessels, aortic cross clamping time, CPB time, and total operative time were also recorded. PO duration of ICU stay, hospital stay, amount of chest tube drainage, and the frequency of PO events were also noted.

The primary endpoint of the current study was the detection of an episode of AF lasting longer than 10 min or the requirement for urgent intervention due to AF as profound symptoms of AF or hemodynamically unstable situations due to AF.

Statistical analysis

Obtained data were presented as mean ± SD, ranges, numbers, and ratios. Results were analyzed using the Wilcoxon ranked test for unrelated data (Z-test) and the χ^2-test. Statistical analysis was conducted using SPSS (version 15, 2006; SPSS Inc., Chicago, Illinois, USA) for Windows statistical package. P value less than 0.05 was considered statistically significant.

Results

The study included 60 patients, 42 male and 18 female with a mean age of 55.1 ± 8.2 years (range 36–68 years). Mean BMI of enrolled patients was 30.3 ± 2.1 kg/m^2. Mean ejection fraction was 48.2 ± 11.1% (range 25–65%); 11 (18.3%) patients had EF of 35% or less, 12 (20%) patients had EF in range of greater than 35–45%, 18 (30%) patients had EF in range of greater than 45–55%, and 19 (31.7%) patients had EF of greater than 55%. There was nonsignificant difference between the studied groups with respect to patients' demographics and clinical profile (Table 1).

Hemodynamic parameters showed nonsignificant difference between the studied groups at times of evaluation throughout surgical intervention (Table 2). Mean ischemia time was 57.9 ± 10.5 min (range 35–75 min); mean CPB time was 78.9 ± 10.8 min (range 58–100 min); and mean total operative time was 175.7 ± 16.5 min (range 145–220 min). The mean number of grafted vessels was 3.9 ± 0.8 (range 3–5 vessels). There was nonsignificant (P>0.05) difference between the studied groups with respect to operative data (Table 3).

All patients passed their PO course without development of Q wave in ECG or PO fever. Eight patients required inotropic support and five patients required defibrillation for resumption of sinus rhythm with nonsignificant difference between the studied groups with respect to the need for inotropic support or defibrillation. Sixteen patients developed POAF for a frequency of 26.7%: eight (40%) patients in group C, five (25%) in group M, and three (15%) in group A. The frequency of patients who developed POAF in group C was significantly higher compared with that of group M (P_1 = 0.041) and group A (P_2 = 0.001), with nonsignificantly (P_3 = 0.083) higher frequency in group M compared with group A (Fig. 1). Four patients developed POAF on the first PO day, two in group C and one in each of the other groups, and the remaining 12 patients developed POAF on the second PO day, six in group C, four in group M, and two in group A, with nonsignificant difference between the studied groups with respect to the timing of occurrence of POAF (Table 4).

The mean duration of mechanical ventilation was 2.03 ± 0.31 h (range 1.5–2.8 h) and the mean amount of chest drainage was 1185 ± 174 ml (range 900–1600 ml) with nonsignificant difference between the studied groups with respect to duration of mechanical ventilation or amount of chest drainage. The mean duration of ICU stay was significantly longer in group C compared with groups M (P_1 = 0.016) and A (P_2 = 0.006), with nonsignificantly (P_3 = 0.480) longer duration in group M compared with group A (Fig. 2). The mean duration of PO hospital stay was significantly longer in group C compared with groups M (P_1 = 0.008) and A (P_2 = 0.004), with nonsignificantly (P_3 = 0.415) longer duration in group M compared with group A (Table 4 and Fig. 3).

Discussion

The applied therapeutic strategy significantly improved the outcome of CABG surgery manifested as significant reduction in the frequency of post-CABG AF with subsequent significant reduction in duration of ICU and hospital stays in comparison with the control group, with nonsignificant difference between groups A and M but in favor of group A. These outcomes point spotlight on the beneficial effects of the additives used for prevention of POAF with subsequent reduction in possibility of development of additional morbidities related to ICU and hospital stays and spare patients and hospital resources.

The obtained results concerning the prophylactic role of magnesium against development of POAF are in agreement with and support those previously reported by Davis *et al.*, who conducted a search of the PubMed database to identify studies published to evaluate the role of pharmacologic strategies beyond β-blockers in the prevention of POAF and found that sufficient evidence exists to recommend the use of magnesium as monotherapy or as add-on therapy for the prevention of POAF.

In addition, Maaroos *et al.* [7] tried to find out how widely different prophylactic strategies for

Table 1 Demographics and clinical profile

Variable	Group C	Group M	Group A	P
Age (years)	53.7 ± 9.6	56.1 ± 9.6	55.4 ± 5.5	P_1 = 0.196 P_2 = 0.301 P_3 = 0.605
Sex (male : female)	14 : 6	13 : 7	15 : 5	P_1 = 0.327 P_2 = 0.403 P_3 = 0.298
Weight (kg)	87.4 ± 2.9	86.6 ± 3.9	86.9 ± 3.4	P_1 = 0.140 P_2 = 0.330 P_3 = 0.634
Height (cm)	169.2 ± 6.1	169.7 ± 5.5	170 ± 6	P_1 = 0.858 P_2 = 0.375 P_3 = 0.385
BMI (kg/m^2)	30.6 ± 2	30.2 ± 2.2	30.1 ± 2.1	P_1 = 0.321 P_2 = 0.391 P_3 = 0.861
Ejection fraction (%)				
Strata [*n* (%)]				
>25–35	3 (15)	4 (20)	4 (20)	P_1 = 0.888 P_2 = 0.686 P_3 = 0.699
>35–45	4 (20)	5 (25)	3 (15)	
>45–55	6 (30)	5 (25)	7 (35)	
>55	7 (35)	6 (30)	6 (30)	
Value	48.9 ± 10.9	47.5 ± 12.3	48.3 ± 10.5	P_1 = 0.059 P_2 = 0.652 P_3 = 0.194

Table 2 Hemodynamic data

Data	Group C	Group M	Group A
Heart rate (beats/min)			
After induction of anesthesia			
Value	75.1 ± 3.5	75.7 ± 5.5	76 ± 3.8
P value		P_1 = 0.528	P_2 = 0.655 P_3 = 0.866
1 h after induction of anesthesia			
Value	77.3 ± 6	78.6 ± 6.5	79.2 ± 6.5
P value		P_1 = 0.243	P_2 = 0.362 P_3 = 0.906
3 h after induction of anesthesia			
Value	79.4 ± 6.5	79 ± 7.2	79.7 ± 7.7
P value		P_1 = 0.909	P_2 = 0.944 P_3 = 0.637
SBP (mmHg)			
After induction of anesthesia			
Value	114.3 ± 7.4	113.7 ± 6.5	112.4 ± 5.1
P value		P_1 = 0.940	P_2 = 0.455 P_3 = 0.614
After CPB weaning			
Value	112.8 ± 7.3	113 ± 5.9	112 ± 5.3
P value		P_1 = 0.879	P_2 = 0.654 P_3 = 0.694
2 h after CPB weaning			
Value	113.3 ± 7.9	113.6 ± 6.8	112.4 ± 6.7
P value		P_1 = 0.856	P_2 = 0.496 P_3 = 0.663
DBP (mmHg)			
After induction of anesthesia			
Value	68.7 ± 5	69.6 ± 7.7	69 ± 7
P value		P_1 = 0.952	P_2 = 0.823 P_3 = 0.694
After CPB weaning			
Value	71.7 ± 7.8	72.2 ± 7.8	74.2 ± 8.7
P value		P_1 = 0.758	P_2 = 0.266 P_3 = 0.492
2 h after CPB weaning			
Value	75.8 ± 8.2	73.4 ± 7.6	75.2 ± 8.6
P value		P_1 = 0.827	P_2 = 0.552 P_3 = 0.381
CVP (mmHg)			
After induction of anesthesia			
Value	8.8 ± 1.5	8.9 ± 1.6	8.6 ± 1.7
P value		P_1 = 0.750	P_2 = 0.758 P_3 = 0.573
After CPB weaning			
Value	10.1 ± 1.6	9.6 ± 1.3	9.9 ± 1
P value		P_1 = 0.133	P_2 = 0.673 P_3 = 0.421
2 h after CPB weaning			
Value	10.5 ± 1.8	10.6 ± 1.9	10.7 ± 1.7
P value		P_1 = 0.740	P_2 = 0.823 P_3 = 0.971

CPB, cardiopulmonary bypass; CVP, central venous pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3 Operative data of studied patients

Data	Group C	Group M	Group A
Aortic cross clamping time (min)			
Value	56.5 ± 8.5	59.1 ± 9.3	58.1 ± 13.5
P value		P_1 = 0.204	P_2 = 0.286 P_3 = 0.926
CPB time (min)			
Value	78.4 ± 14.7	77.5 ± 7.8	80.8 ± 9
P value		P_1 = 0.751	P_2 = 0.445 P_3 = 0.304
Duration of surgery (min)			
Value	175.2 ± 18.3	174.2 ± 10.4	177.7 ± 19.9
P value		P_1 = 0.808	P_2 = 0.601 P_3 = 0.390
Number of grafted vessels			
Value	3.85 ± 0.8	4 ± 0.7	3.8 ± 0.9
P value		P_1 = 0.405	P_2 = 0.787 P_3 = 0.632

CPB, cardiopulmonary bypass.

Table 4 Postoperative data of studied patients

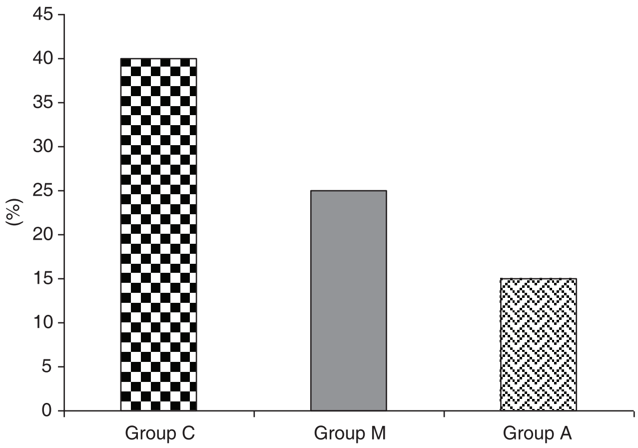
Data	Group C	Group M	Group A
Development of new Q wave in ECG	0	0	0
Development of POAF			
Frequency [*n* (%)]	8 (40)	5 (25)	3 (15)
P value		P_1 = 0.041	P_2 = 0.001 P_3 = 0.083
Defibrillation			
Frequency [*n* (%)]	2 (10)	2 (10)	1 (5)
P value		P_1 = 0	P_2 = 0.091 P_3 = 0.091
Inotropic support			
Frequency [*n* (%)]	3 (15)	2 (10)	3 (15)
P value		P_1 = 0.067	P_2 = 0 P_3 = 0.067
Duration of mechanical ventilation (h)			
Value	1.99 ± 0.31	2.06 ± 0.28	2.04 ± 0.35
P value		P_1 = 0.500	P_2 = 0.722 P_3 = 0.904
Amount of chest tube drainage (ml)			
Value	1165 ± 166.8	1205 ± 171.6	1185 ± 189.3
P value		P_1 = 0.431	P_2 = 0.722 P_3 = 0.686
Development of postoperative fever	0	0	0
ICU stay (h)			
Value	76.2 ± 11.6	71.7 ± 10.9	69.3 ± 9
P value		P_1 = 0.016	P_2 = 0.006 P_3 = 0.480
PO hospital stay (days)			
Value	6.7 ± 0.9	5.9 ± 0.8	5.7 ± 0.9
P value		P_1 = 0.008	P_2 = 0.004 P_3 = 0.415

PO, postoperative; POAF, postoperative atrial fibrillation.

POAF are used in Scandinavian countries and found that magnesium was used by 17% of cardiac surgeons as prophylactic measure for POAF. Khalil *et al.* [8] reported significantly lower incidences of AF in patients undergoing lobectomy and receiving prophylactic amiodarone alone or magnesium sulfate alone compared with control patients, with no significant difference between the amiodarone (10%) and magnesium sulfate (12.5%) groups, and there were significant differences between the three groups concerning ICU and total hospital stays.

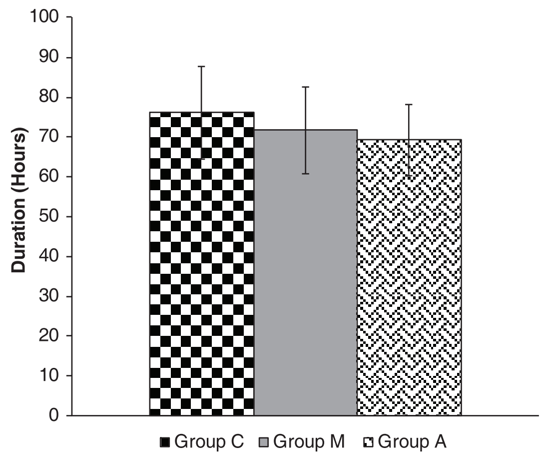
Multiple studies denied the prophylactic effect of magnesium against the development of POAF [9–11]; however, these studies depended on the revision of previous published works either as comparative or noncomparative studies and suggested that conclusion. In support of this explanation for the difference of effect of magnesium on POAF, Arsenault *et al.* [12] in Cochrane study concluded that prophylaxis to prevent AF after cardiac surgery with any of the studied pharmacological or nonpharmacological

Figure 1



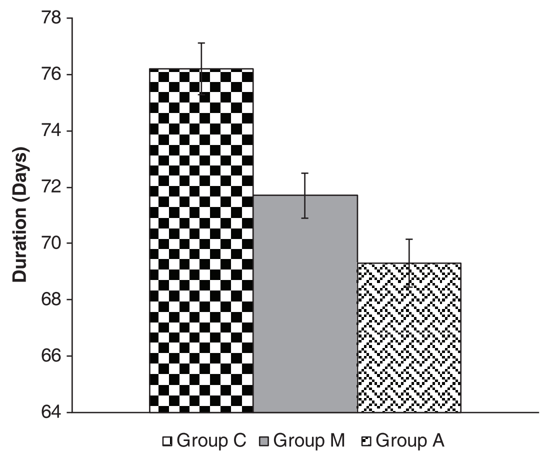
Frequency of postoperative atrial fibrillation (AF) in the studied groups.

Figure 2



Mean ± SD postoperative ICU stay duration of patients of the studied groups.

Figure 3



Mean postoperative hospital stay duration of patients of the studied groups.

interventions may be favored because of its reduction in the rate of AF, decrease in the length of stay and cost of hospital treatment, and a possible decrease in the rate of stroke.

However, this review is limited by the quality of the available data and heterogeneity between the included studies, and selection of appropriate interventions may depend on the individual patient situation and should take into consideration adverse effects and the cost associated with each approach [12].

With respect to ascorbic acid prophylaxis against development of POAF, Papoulidis *et al.* [13] found that supplementation of vitamin C significantly reduced the incidence of AF, the hospitalization time, the ICU stay, and the time interval for the conversion of AF into sinus rhythm. Harling *et al.* [14] reported that vitamins C and E significantly reduced the incidence of POAF and all-cause arrhythmia compared with controls, with a significant reduction in both ICU stay and hospital stay in the antioxidant group. Rasoli *et al.* [15] conducted a review of the literature concerning the use of antioxidants for prophylaxis against POAF and found that four studies showed antioxidant vitamins to significantly reduce the incidence of POAF and two studies showed that prophylactic treatment with adjuvant vitamin C and β-blockers is more effective than β-blocker therapy alone.

In addition, Rebrova *et al.* [16] found that administration of ascorbic acid at the stage of preparation of patients to surgery and in first 24 h after operation effectively prevented development of oxidative stress and disturbances of cardiac rhythm after CABG surgery and concluded that inclusion of ascorbic acid in drug therapy of patients with ischemic heart disease could be recommended for prevention of arrhythmia during PO period. Rodrigo *et al.* [17] found that the reinforcement of the antioxidant system through n-3 polyunsaturated fatty acids and vitamin C and E supplementation is a safe, well tolerated, and low-cost regimen that favorably reduces the incidence of POAF, increases antioxidant potential, and attenuates oxidative stress and inflammation.

In contrast to the obtained results concerning the use of vitamin C, Bjordahl *et al.* [18] found that supplementation of ascorbic acid in addition to routine PO care does not reduce AF after CABG. However, such difference of effect could be attributed to the PO administration of ascorbic acid, whereas the current study used ascorbic acid as prophylaxis after induction of anesthesia and before any manipulation that could help to release ROS; thus, prophylaxis use could strengthen the antioxidant system before the insult. Thereafter, ascorbic acid was used throughout 5 days after surgery to continue the supplementing effect to the antioxidant system.

In support of the beneficial effects of prophylaxis by vitamin C, Fukushima and Yamazaki [19] reported that blood vitamin C concentration decreases after uncomplicated elective surgery with further decreases in surgical ICU patients and attributed this decline to increased demand caused by increased oxidative stress and recommended the use of much higher doses than the recommended daily allowance or doses recommended in parenteral nutrition guidelines to normalize plasma vitamin C concentration with much higher doses in surgical ICU patients.

The reported results and review of the literature allowed concluding that prophylactic use of ascorbic acid or magnesium significantly reduced the frequency of POAF after CABG surgery and significantly reduced ICU and hospital stay. However, wider scale studies are advocated for confirmation of these results, especially those concerning magnesium, and to evaluate the outcome of combined administration of both for the frequency of POAF.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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