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F.Ü.Sağ.Bil.Vet.Derg.
2018; 32 (1): 07 - 12
http://www.fusabil.org

Effect(s) of Long-Term Anaesthesia Induced by Isoflurane, Sevoflurane, Propofol-Fentanyl, Medetomidin-Midozolam-Ketamine or Xylazine-Ketamine Combinations on the Acut Phase Proteins and Cardiac Troponins Levels in Rabbits *

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The aim of this study was to determine the effect(s) of long-time anesthesia generated by isoflurane, sevoflurane, propofol-fentanyl, medetomidine-midozolam-ketamine or xylazine-ketamine combinations on hemodynamic parameters, serum cardiac troponin-I, and C-reactive protein concentrations in rabbits. The study was performed on 30 New Zeland rabbits. Rabbits were divided into 5 groups. In group 1, induction was performed with isoflurane, and anesthesia lasted for four hours. In group 2, the same procedure in group 1 was applied using sevoflurane instead. In group 3, midazolam, medetomidine and ketamine were administered intramuscularly. Anaesthesia protocols lasted for four hours with additional injections. In group 4, anaesthesia was induced with fentanyl and propofol and maintained with fentanyl and propofol) for four hours. In group 5, xylazine were used for premedication. General anesthesia was performed with ketamine. Four hour anesthesia was maintained. The reflexes between induction and recovery time were evaluated. Haemodynamic and respiratory variables were recorded. Blood samples were analyzed for biochemical parameters (CRP and cTn-I).

While group 5 or group 3 protocols provided analgesia for major surgical approaches, group 1 and group 2 anaesthetics were enough for minor surgical approaches. In group 2 and group 3, heart rates decreased compared to pre-induction. When we measured the CRP and cTn-I serum levels before, during and after 6, 12 and 24 hours of induction, no significant change in values observed in between the groups. In conclusion, cardiac troponins could be used to detect acute myocardial damage associated with anesthesia both experimental and clinical studies.

Key Words: *Cardiac troponin-I, CRP, isoflurane, sevoflurane, midazolam, ketamine, propofol, fentanyl, rabbit*

Tavşanlarda İzofluran, Sevofluran, Propofol-Fentanil, Medetomidin-Midazolam-Ketamin ve Ksilazin-Ketamin ile Oluşturulan Uzun Süreli Anestezinin Akut Faz Proteinleri ve Kardiyak Troponin I Konsantrasyonları Üzerine Etkisi

Bu çalışmada, kalp üzerine olumsuz etkileri bilinen enjektabl anestezik kombinasyonlardan medetomidin-ketamin-midazolam ve ksilazin-ketamin ile kardiyoprotektif etkileri bilinen inhalasyon anesteziklerinden izofluran ve sevofluran ile enjektable anesteziklerden propofol-fentanil kombinasyonlarının kalp üzerindeki olası yan etkilerinin göstergesi olan kardiyak troponin I ve C-reaktif (CRP) proteinin düzeylerinin karşılaştırmalı olarak araştırılması amaçlanmıştır. Hayvan materyalini 15 erkek ve 15 dişi olmak üzere toplam 30 adet erişkin Yeni Zelanda tavşanı oluşturdu. Tavşanlar altışarlı 5 gruba ayrıldı. Bu amaçla 1. gruptaki tavşanlara izofluran ile 4 saatlik anestezi sağlandı. 2. gruptaki hayvanlara ise 1. gruptakiyle aynı prosedür sevofluran kullanılarak uygulandı. 3. gruptaki hayvanlara ise başlangıçta midazolam, medetomidine and fentanyl i.m. uygulanarak takiben ek doz uygulaması ile toplam 4 saatlik bir anestezi oluşturuldu. 4. gruptaki hayvanlara ise fentanil ve propofol ile indüksiyonunu takiben genel anestezinin idamesi propofol ve fentanil ile toplam 4 saatlik bir anestezi sağlandı. Son gruptaki hayvanlara ksilazin ile premedike edilerek ketamine ile 4 saatlik anestezi oluşturuldu. Ayrıca her tavşan için anestezi öncesi, sırası ve sonrasında refleksler, kalp atım sayısı, solunum sayısı ve biyokimyasal (CRP and cTn-I) parametreler kayıt edildi.

5. grup ve 3. grup kombinasyonları major cerrahi prosedürler için uygun bulunurken 1. grup ve 2. grup anestezi protokolleri ise minor cerrahi prosedürler için daha uygun bulundu. Kalp atım sayısında 2. grupta ve 3. grupta başlangıç değerlerine göre azalma istatiksel olarak anlamlı bulundu. CRP ve cTn-I değerlerinde, gruplar arasında ve başlangıç değerlerine göre istatiksel olarak analizleri yapıldı; ancak anlamlı bir fark belirlenmedi. Sonuç olarak, kardiyak troponinler uzun süreli anesteziye bağlı oluşabilecek akut miyokardiyal hasarın erken belirlenmesinde kullanılabileceği kanısına varılmıştır.

Anahtar Kelimeler*: Cardiac troponin-I, CRP, izofluran, sevofluran, midazolam, ketamin, propofol, fentanil, tavşan*

The Arrival Date : 30.11.2017
Acceptance Date : 29.12.2017

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* This study was supported by the Adnan Menderes University Scientific Research Foundation (Project number: VTF-14005).

Introduction

Rabbits are common laboratory animals in many research institutions. Anaeshetic procedures are required for many of these experiments. However, these approaches can cause many side effects including high mortality rate (1/72) (1).

The main concerns in appropriate anaesthetic administration are to have a safe and reliable anaesthetic effect with minimal dosage of anaesthetic agents and to minimize the hemodinamic and cardiovascular complications. Myocardial injuries are amongst common complications during anaesthesia or other ischemic disorders (2). There is evidence that preconditioning heart for ischemic conditions can be a protector factor to the heart itself and others from severe ischemic situations (3). Indeed, there are anaesthetic agents with protective impacts on myocardial, renal and cerebral tissues during anaesthesia (4).

Volatile anaesthetic agents such as isoflurane and sevoflurane induce the repair of the myocardial tissue and protect it by increasing reperfusion. Decreasing heart rate and myocardial contractility may be favorable alterations for myocardium by diminishing its oxygen demands and the infarct size (5). On the other hand, the injectable anaesthetics like propofol and fentanyl are accepted as "less protective" for myocard (6). Although its degree varies according to myocardial ischemia or mechanism and anesthesia type, it is possible to preserve the myocardium during anaesthesia in many species (7).

There are several markers to determine the myocardial damage. Myoglobin, which is one of the such a marker is an indicator of myocyte damage however it is not specific for the tissue (8). Similar to myoglobin, creatine phosphokinase isoenzyme used for the diagnosis of myocardial infarction, also is not specific for myocardial damage as it is found in other tissues and organs such as skeletal muscle, vascular muscle, brain, uterus and placenta (9). It is now possible to determine myocardial damage by measuring highly specific cardiac structural proteins such as troponins (10-12). Compared to other cardiac markers, cardiac troponins are more useful in determining heart damage. Cardiac troponin is a specific and highly sensitive marker of myocardial injury (13). These markers have made it possible to diagnose heart diseases more accurately and earlier. Early diagnosis and early treatment of myocardial injury is very important for the prognosis (12, 14). There are several studies on troponin (Tn) levels in cardiomyopathy patients and its relation to prognosis (11).

The main objective of this study was to determine the possible effect(s) of long-time anesthesia by isoflurane, sevoflurane, propofol-fentanyl, medetomidine-midozolam-ketamine and xylazine combinations on myocardial tissue by measuring hemodynamic parameters, serum cTn-I and CRP concentrations in rabbits.

Materials and Methods

Animals: In this study, 15 female and 15 male New Zealand rabbits weighting between 2 and 4 kg were employed. All rabbits were obtained from a breeding farm with certification, and housed in separate pens individually for acclimatizing new environment for 2 weeks. The room temperature (16-19 °C), humidity (50-60%) and light and dark rate (12:12 hours) were arranged. All rabbits had access to rabbit pellet diet and water ad libitum. They were also given washed carrot and dried bread.

All experiments were approved by Adnan Menderes University Local Board of Ethics Committe for Animal Experiments (Number-64583101/2013/81).

Monitoring of the Reflexes: The main reflexes (standing, ear and finger) of each individual rabbit were evaluated in five minutes intervals before, during and after the administration processes and recorded. The durations of the surgical anesthesia and total sedation times were recorded. To avoid eye dryness, Viscotears® were used for the eyes to while they were sleeping.

Anesthesia Protocols: Thirty rabbits were randomly separated into five groups consisting of three males and three 3 females. Twenty-four hours before the examinations, weights, body temperatures, pulses and respiratoric rates of each animals were recorded. Rabbits showing abnormal physiological findings were excluded from the study.

All examinations were performed between the hours of 9:00-13:00 in each day during the study. In group 1, induction was performed with isoflurane by using face mask. Induction was noted and endotracheal intubation of the airways was performed. The tube was connected to the anaesthesia machine and anesthesia was lasted for four hours. In group 2 the same procedure in group 1 was applied using sevoflurane instead. In group 3, midazolam (1.0 mg/kg), medetomidine (0.05 mg/kg) and ketamine (20 mg/kg) were administered intramuscularly. Anaesthesia protocols were lasted for four hours with additional injections. In some animals anesthesia was completely reversed by using the chemical antagonists, flumazenil (0.1 mg/kg) and atipamezole (0.5 mg/kg), injected subcutaneously. In group 4, anaesthesia was induced with fentanyl (0.0053 mg/kg) and propofol (4-8 mg/kg) and maintained with fentanyl (0.48 µ/kg/min) and propofol (0.6 mg/kg/min) for four hours. In group 5 xylazine (5 mg/kg) were used for premedication. General anesthesia was performed with ketamine (5 mg/kg). Four hours anesthesia was maintained using half dose of the first administration dose.

During the applications *V. auricularis magna* was used. It was catheterized with 22 g catheter (NovaCath®) and to avoid catheter obstruction %0.9 NaCl was administered with heparinized (Nevparin®) syrings to the catheter after each application.

Monitoring Clinic Parameters: Body temperatures observed with digital termometer (Nimo®), respiratory rates were noted and tail was clipped for placement of a pulse oximeter probe for measuring oxygen saturation (SpO_2) with monitor (PETAS KMA® 275). Data were collected at preanesthesia, induction (0 min) and 5, 10, 15, 30, 45, 60, 120, 180, 240 mins after the induction.

Laboratory Tests: Blood samples (2 mL each) were collected from marginal ear vein before (0 time), during and after 6, 12 and 24 hours of induction for measurement of CRP and cTn-I. Blood samples were allowed to analysis of CRP and cTn-I.

Serum CRP: Serum CRP was measured by Rabbit CRP Elisa Kit, commercially available from CUSABIO Biotech Co., Ltd. (Cat No: CSB-E06847Rb). The assay was performed according to the manufacturer's instructions. ELISA plates were pre-coated with rabbit CRP. Colour was developed with TMB substrate and absorbance was measured at 450 nm against standard curves. Mean values were reported. The sensitivity of the assay was 2 pg/mL. The detection range was 7.8 pg/mL-2000 pg/mL. Intra-assay and inter-assay coefficient of variations were <8% and <10%, respectively.

Serum Cardiac Troponin I (cTn-I): Serum cTn-I was measured by rabbit cardiac troponin I (cTn-I) Elisa Kit, commercially available from CUSABIO Biotech Co., Ltd. (Cat No: CSB-E11286Rb). The assay was performed according to the manufacturer's instructions. ELISA plates were pre-coated with anti-rabbit cTn-I antibody. Colour was developed with TMB substrate and absorbance was measured at 450 nm against standard curves. Mean values were reported. The sensitivity of the assay was <11.75 pg/mL. The detection range was 47 pg/ml-3000 pg/mL. Intra-assay and inter-assay coefficient of variations were <8% and <10%, respectively.

Results

Clinical and Biochemical Parameters: In animals, sedation occurred within 6±0.64 secs in group 4, whereas it was even quicker in group 3 (5±0.47 secs). Sedation took longer in group 1 and group 2 (Table 1). Maintenance of anaesthesia was characterized by muscle relaxation and loss of the pedal withdrawal reflex. However it was shorter in isoflurane and sevoflurane groups (Group 1 and 2, respectively) due to the weak analgesic effects of these anaesthetics. After recovery, righting reflex returned in all animals and they began to eat as soon as they were put in their cages.

When respiratory rates were evaluated between groups, the rate decreased significantly in propofol-fentanyl group at 5, 45 and 60 minutes compared to the others (Table 2). In group 4, the respiratory rates started to decrease at earlier time points in group 5 compared to the groups 1 and 2. The respiratory rates of animals in group 2 stayed highest at all time points during anaesthesia compared to the animals in other groups (Table 2). O_2 saturation dropped below 80% in group 5 (Table 2). Only in group 3 the body temperature of the rabbits measured below 37 ^{0}C after 120 min of anaesthesia (Table 2).

When the changes in heart rate between groups were examined, there was a statistically significant decrease in group 3 compared to group 4 and 2 at 120, 180 and 240 minutes (Table 2). The most significant decrease was observed in ketamine-medetomidine-midazolam group at 180 mins (Table 2).

When we measured the CRP and cTn-I serum levels before, during and after 6, 12 and 24 hours of induction no significant change in values observed in any of the groups (Table 3).

Tablo 1. The times for loss of the reflexes in the groups

Reflexes (Disappear Time)	Groups				
	1	2	3	4	5
Standing reflex (sec)	6±0.64	5±0.47	6±0.96	185±63.87	167±57.13
Ear pinch (sec)	965±113.82	652±92.44	147±23.75	425±24.72	786±21.37
Tail pinch (sec)	758±34.68	378±75.27	235±43.85	985±156.46	895±46.78
Front linb (toe pinch) (sec)	2732±256.75	563±92.15	425±84.75	2693±284.17	3327±340.12
Hind limb (toe pinch) (sec)	3541±276.65	637±78.15	513±47.32	3654±324.96	3548±456.32
Pupillar reflex (sec)	23±0.45	15±0.32	11±0.6	395±13.74	232±42.31

Tablo 2. Effects of different anaesthesia groups on body temperature, respiatory rate, heart rate and haemoglobin oxygen saturation over time

Variable	Groups	Time (min) 0	15	30	45	60	180	240
T (°C)	1	38.53±0.23^{a}	38.72±0.21^{a}	38.72±0.32^{a}	38.23±0.33^{ab}	38.03±0.34^{a†}	38.12±0.18^{a†}	38.12±0.15^{a†}
	2	38.68±0.46^{a}	38.33±0.49^{a}	38.33±0.31^{a}	37.67±0.50^{a†}	37.11±0.40^{b†}	36.10±0.48^{b†}	36.10±0.78^{b†}
	3	38.78±0.23^{a}	39.53±0.29^{bc†}	39.53±0.21^{b†}	38.97±0.28^{b}	38.97±0.26^{ac†}	38.32±0.52^{ac}	38.32±0.67^{abc}
	4	39.25±0.31^{ab}	38.85±0.29^{b}	38.85±0.14^{b}	39.10±0.24^{c}	38.92±0.33^{c}	39.00±0.19^{c}	39.00±0.21^{c}
	5	39.63±0.14^{b}	39.667±0.19^{c}	39.67±0.26^{b}	39.65±0.39^{bc}	39.73±0.42^{c}	39.267±0.20^{c}	39.27±0.35^{ac}
f_R (respiration/ min)	1	146.00±22.72^{ac}	59.50±25.45^{a}	36.50±6.89^{a†}	35.33±6.30^{a†}	38.33±6.64^{a†}	41.33±5.60^{a†}	56.50±13.65^{ab†}
	2	115.67±18.33^{bc}	58.00±5.24^{b}	65.00±11.24^{ab†}	65.33±4.81^{b†}	61.33±2.23^{b}	50.83±4.97^{ab†}	53.00±3.97^{a†}
	3	183.33±20.35^{a}	64.33±9.44^{ab†}	80.17±18.06^{ab†}	74.67±9.73^{b††}	82.00±21.34^{b†}	58.67±17.99^{ab†}	71.33±25.85^{ab†}
	4	108.67±20.64^{c}	86.33±9.39^{a}	82.67±17.67^{b}	82.33±10.33^{b}	72.00±8.82^{b}	70.67±11.11^{b}	82.67±7.4^{b}
	5	107.00±18.55^{c}	91.17±19.42^{ab}	77.50±15.91^{b}	65.00±12.67^{b}	82.50±26.23^{b}	71.33±22.71^{ab}	67.83±10.09^{ab†}
f_H (beats/ min)	1	160.00±23.25	159.50±19.77	165.00±15.88	165.50±15.53	172.33±17.76^{ab}	187.67±11.57^{a}	196.17±13.68^{a}
	2	185.00±16.87	160.67±19.64	152.67±34.77	144.33±20.54	133.33±26.79^{ab}	106.67±17.20^{b†}	131.33±6.90^{b†}
	3	227.67±24.56	161.00±19.91†	156.50±24.82	155.00±25.50	121.33±20.85^{a†}	155.50±20.90^{ab}	151.50±21.43^{ab†}
	4	194.83±16.31	193.67±19.43	172.67±10.67	188.83±21.10	199.00±14.86^{b}	186.83±16.11^{a}	187.83±15.59^{a}
	5	172.67±5.86	181.50±14.33	147.33±14.49	164.33±15.02	168.33±7.23^{ab}	182.00±25.29^{a}	155.83±25.62^{ab}
SpO_2 (%)	1	98.00±0	98.00±0^{a}	98.00±0^{a}	98.00±0^{a}	98.00±0^{a}	98.00±0^{a}	98.00±0^{a}
	2	98.00±0	98.00±0^{a}	98.00±0^{a}	98.00±0^{a}	98.00±0^{a}	96.83±0.75^{a}	97.33±0.5^{a}
	3	85.83±4.44	84.00±3.14^{b}	84.50±3.66^{b}	77.50±5.14^{b}	76.33± 5.42^{b}	88.83±5.43^{b}	91.50±2.95^{bc}
	4	98.67±1.17	96.33±2.28^{a}	94.00±2.10^{a}	94.83±2.20^{a}	94.33±2.06^{c}	95.33±1.09^{a}	96.17±0.83^{ab}
	5	98.67±3.57	94.50±2.28^{a}	94.33±2.57^{a}	94.50±3.32^{a}	97.33±1.05^{ac}	90.50±6.93^{c}	92.17±5.07^{c}

T: Temperature; f_R: Respiatory rate; f_H: Heart rate; SpO_2: Haemoglobin oxygen saturation; Min: Minutes.

†: Mean values differ significantly from baseline (preanesthesia) (P<0.05)

a,b,c,d,e: The different letters in the same column differ significantly (P<0.05)

Table 3. Changes in CRP and cTnI over time

Groups	CRP (pg/mL) Time 0	160 min	6 hr	12 hr	24 hr	cTn I (ng/mL) 0	160 min	6 hr	12 hr	24 hr
1	2.81±0.20	2.53±0.22	2.89±0.19	2.69±0.25	2.97±0.19	5.25±1.28	6.12±1.28	6.85±0.41	6.50±0.80	7.06±0.46
2	2.24±0.08	2.19±0.11	2.09±0.21	2.05±0.16	2.14±0.21	5.31±0.44	5.63±0.16	4.08±0.83	4.81±0.76	5.56±0.40
3	2.71±0.22	2.64±0.31	2.48±0.30	2.48±0.24	2.83±0.28	6.50±0.63	6.01±0.81	6.01±0.97	5.67±0.57	6.64±1.21
4	2.57±0.33	2.62±0.17	2.68±0.23	2.20±0.20	2.38±0.18	8.27±1.10	6.15±1.29	7.25±0.71	8.08±0.93	7.90±0.93
5	2.18±0.19	2.31±0.18	2.25±0.21	2.01±0.43	2.20±0.27	7.89±0.81	8.46±0.98	6.14±1.45	6.33±1.34	8.61±1.02

Discussion

Kılıç et al. (15) reported that the disappearance of the righting reflex duration in rabbits anesthetised with IM medetomidine-ketamine (0.25 mg/kg medetomidine, 50 mg/kg ketamine) was 1.8±0.4 mins after induction and total anesthesia duration was 150±30 mins. In the same study, the plantar reflex disappearance duration was 50±28 minutes and surgical anesthesia lasted 45±26 minutes. In a similar study by Henke et al. (16) reported that in IM 0.25 mg/kg ketamine and 35 mg/kg ketamine administered-rabbits loss of righting reflex 1.7±0.4 was mins after injection and the total anesthesia duration was 149.7±38.7 mins with 70.2±25.5 mins duration for plantar reflex disappearance and 38.7±30.0 mins long surgical anesthesia. In our study, all reflexes in animals disappeared earlier than the previously mentioned studies as all sedative and anesthesic agents given intravenously. Indeed, the effects of anaesthetic and sedative agents administered intravenously occur in a shorter time, meanwhile the anaesthetic or sedative effects are also shorter compared to the intramuscular or subcutanous routs (15).

Mazaheri-Khameneh et al. (17) reported that the duration of disappearance of the righting reflex after induction of propofol (12.5 mg/kg induction; 1 mg/kg/min, 30 min) was 9±0.81 secs in rabbits and the total anesthesia duration was 37±0.96 mins.

In our study ketamine-xylazine administration decreased respiratory rates of the animals at earlier time points compared to the other groups. Ketamine can

cause temporary apnea in animals due to administration dosage. At higher doses, apneic, superficial and irregular respiration occurs (19).

Pal et al. (20) reported that respiratory rates of rabbits decreased significantly after 10-20 minutes, following the administration of combination of ketamine with xylazine, acepromazine or medetomidine. Similar findings were found in a study (21) in which propofol was administered intravenously in rabbits. According to Ponte and Sadler (22), propofol reduces the respiratory rate and tidal volume, and is a chemodepressor that decreases the ventilation response to hypoxia with increasing infusion rate. In our study, oxygen saturation stayed same in propofol-fentanyl group at all time points whereas it decreased in xylazine-ketamine group and at 180 and 240 mins (Table 2). There was a statistically significant decrease in ketamine compared to other anesthesia groups.

Hess et al. (23) administered medetomidine and naphthalene analog naftilmedetomidine, intravenously to rabbits and found that oxygen saturation dropped significantly in the rabbits given medetomidine for 3 minutes after administration. Grint and Pamela (24) compared ketamine-midazolam and ketamine-medetomidine anesthesia in a study where they mixed the drugs in the same injector and after applying them intramuscullary they entubated the rabbits and examined some parameters. Although the rabbits were entubated, the oxygen saturation of the animals in the medetomidine-ketamine group was 93-99% (average 96). In our study, oxygen saturation after ketamine and xylazine injections fell below 85%, indicating the necessity of endotracheal entubation in prolonged anesthesia. Cruz et al. (25) observed a similar decrease in oxygen saturation in animals where they were given a propofol infusion in a similar study in rabbits, and a parallel increase in saturation was observed at forthcoming. Wiese et al. (18) reported that in a study performed in cats, propofol was significantly reduced at higher doses compared to baseline oxygen saturation as a result of infusion and then returned to baseline values.

One of the most important complications in prolonged anesthesia is hypothermia. In our study, the duration of anesthesia was one hour. Body temperatures of rabbits stayed stable with a slight increase at all groups but Ketamine-medetomidine-midazolam where they decreased significantly below 37 ^{0} C after 120 mins (Table 2).

The heart rates in the group 3 at 120 ($P<0.05$), 180 ($P<0.05$) and 240 mins ($P<0.05$) compared to group's baseline values were statistically significant. Similar findings observed with group 5 for 240 mins vs group's baseline values.

When serum cTnI and CRP levels were evaluated against in-group baseline values we observed no significant change at 24 hours period (during and after sedation) in any of the animals.

Effects on serum cTn-I concentrations of anesthesia in horses during MR exposures was investigated by Slack at al. (26) in a clinical trial. Similar to our findings they reported no significant change in cTn-I level in the first postoperative 24 hours. Singletary et al. (27) showed similar results in dogs sedated intravenously with medetomidine (10 µg/kg) and butorphenol (0.2 mg/kg) combination. On the other hand, a study by Cilli at al. (28) comparing serum cTn-I levels after various anesthesia protocols in 107 dogs with different races and different health status reported that cTn-I levels increased in 14% of the dogs in the postanaesthetic period whichmay be caused by bleeding, some hypoxic periods during the surgical procedures and excessive changes occasionally occurring in the pulse and blood pressure.

In conclusion, we suggest that cTn-I can be used both in experimental and clinical studies to detect early myocardial damage associated with anesthesia. We hope that these markers can be used clinically in different animal species.

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