

Comparative study on the clinical profile of different doses of dexmedetomidine with levobupivacaine in supraclavicular brachial plexus block

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Abstract

Background and aims: Many studies have been conducted using dexmedetomidine as adjuvant to local anaesthetics in peripheral nerve blocks, but few studies compare the effect of different doses of dexmedetomidine. We aimed at comparing the clinical profile of different doses of dexmedetomidine as adjuvant to levobupivacaine in supraclavicular brachial plexus block and finding out the dose which provides maximum improvement in block parameters with minimum undesirable effects.

Material and Methods: This double blinded comparative study was conducted in 120 patients belonging to American Society of Anaesthesiologist Physical Status (ASA PS) I or II, undergoing elective upper limb orthopaedic procedures. The subjects were randomly allocated into four groups of 30 each. Supraclavicular brachial plexus blocks were performed in each group. While group LS received plain levobupivacaine, group LD30, LD60 and LD100 received 30 microgram(mcg), 60mcg and 100mcg dexmedetomidine along with levobupivacaine. The primary outcomes studied were block parameters and the secondary outcomes were hemodynamic profile, oxygen saturation and sedation scores. Statistical analysis was done using ANOVA test, chi-square test and Scheffe's multiple comparison tests.

Results: The demographic profile and hemodynamic variables were comparable in all four groups. Increasing doses of dexmedetomidine showed statistically significant improvement in block parameters and increase in sedation score, while significant decrease was found in heart rate and blood pressure.

Conclusions: A dose of 60mcg of dexmedetomidine showed clinically significant improvement in block characteristics with minimum undesirable effects like bradycardia, sedation and prolonged motor blockade.

Keywords: Dexmedetomidine, Levobupivacaine, Supraclavicular brachial plexus block.

Key Messages: A dose of 60mcg dexmedetomidine as adjuvant to local anaesthetics in supraclavicular brachial plexus block provides best block characteristics with minimum side effects.

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Introduction

Peripheral nerve blocks, in orthopaedic surgical procedures, have the advantage of good intra and post-operative analgesia and improved patient comfort. Even though supraclavicular brachial plexus block provides fast, complete and dense analgesia for upper limb procedures,^[1] The effect tends to wear off rapidly due to high vascularity of the site. To overcome this, several adjuvants are used among which dexmedetomidine has achieved considerable popularity recently.

Although there are several studies showing the efficacy of dexmedetomidine as an adjuvant, there is no clear consensus regarding an ideal dose to be used. In this study, we are trying to find out an optimum dose of dexmedetomidine which provides maximum improvement in block characteristics with minimum untoward effects.

Methods

After obtaining institutional ethics committee approval, 120 patients of ASA PS I/II belonging to either sex, aged 18-50 years weighing between 50 - 70kgs scheduled for elective upper limb surgeries of mid arm and fore arm were enrolled in this prospective study with written informed consent. Patients with cardiac disease, hepatic or renal impairment, neuromuscular disorders, uncontrolled hypertension or diabetes mellitus, pregnancy, coagulopathy, known hypersensitivity to local anaesthetics, and on adrenergic agonist/antagonist medications were excluded from the study.

These patients were allocated into four groups of 30 each (LS, LD₃₀, LD₆₀ and LD₁₀₀) using slips in box technique. The patients and the anaesthesiologists performing blocks and assessing patients were blinded to the study groups. The drug solutions were prepared by an anaesthesiologist blinded to the study groups and not involved in the study. After securing a patent intravenous cannula on the non-operating hand, baseline heart rate(HR), non-invasive blood pressure (systolic(SBP) and diastolic(DBP)) and oxygen saturation were recorded(SpO₂).ECG and SpO₂ were monitored continuously and blood pressure was monitored every five minutes. Supraclavicular block

was performed by subclavian perivascular approach using peripheral nerve stimulator (Stimuplex, B/Braun, Germany) with 22G, 5cm needle. The end point was a motor response of fingers with a current of 0.5mA.

Group LS received 2.5mg/kg of plain levobupivacaine made up to 40ml with normal saline. Groups LD30, LD60 and LD100 received 30mcg, 60mcg and 100 mcg of dexmedetomidine respectively along with levobupivacaine and total volume was made up to 40ml with normal saline. The purpose of selecting patients with weight between 50-70kg was to make the doses of dexmedetomidine correspond approximately to 0.5mcg/kg (30mcg), 1mcg/kg (60mcg) and 1.5mcg/kg (100mcg).

Both sensory and motor block were assessed every 3 minutes till their onset and every 30 minutes after the completion of the procedure till the blocks were resolved. The subjective recovery of sensations, movement and pain were noticed by the patients and informed to the concerned anaesthesiologists. HR, SBP, DBP and SpO₂ were recorded at 0 minute (immediately after drug administration) and then 5, 10, 15, 30, 45, 60, 90 and 120 minutes from the time of drug administration. Sedation was assessed every 15 minutes after the administration of drug for the first one hour and the maximum score during this period was recorded according to modified Ramsay sedation scale.

Modified Ramsay sedation scale

- 1- Patient is anxious and agitated or restless or both
- 2 -Patient is co-operative, oriented and tranquil
- 3 -Patient responds to commands only
- 4 -Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
- 5 -Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
- 6 -Patient exhibits no response

Patients who were having a sedation score of 1 at the end of first hour were sedated with one milligram midazolam.

Sensory block was assessed by pinprick on all four nerve territories i.e., ulnar, radial, median and musculocutaneous, using a 3 point scale (0 – normal sensation, 1- loss of pin prick sensation, 2- loss of touch sensation). Motor block was assessed by thumb abduction (radial nerve), adduction (ulnar nerve), opposition (median nerve) and flexion of elbow (musculocutaneous nerve) according to modified Bromage scale.

Grade 0 – Normal motor function with full movement of elbow, wrist and fingers.

Grade 1 – Decreased motor strength with ability to move fingers only.

Grade 2 - Complete motor block with inability to move fingers.

Onset time of sensory block was defined as the time interval between the end of local anaesthetic administration and onset of complete sensory block (minimum score of 1 on all four nerve territories).

Duration of sensory block was defined as time interval between the onset of complete sensory block and complete recovery of sensations on all four nerve territories (grade 0).

Onset time of motor block was defined as the interval between end of local anaesthetic administration and onset of complete motor block (at least grade 1 on all four nerve territories). Duration of motor block was defined as the interval between onset of complete motor block and complete recovery of motor function (grade 0).

Duration of analgesia was defined as the interval between the onset of complete sensory block and the time at which subjective sensation of pain was first felt.

Hypotension was defined as BP less than 30% of baseline and was managed with injection mephentermine 6mg intravenously (IV). Bradycardia was defined as heart rate less than 50/min and was managed with injection atropine 0.6mg IV. Hypoxia was defined as SpO₂ less than 90%. Patients were watched for any other side effects like nausea, vomiting, respiratory depression, local anaesthetic toxicity. Blood loss exceeding maximum allowable blood loss (MABL) was planned to be corrected with blood transfusion. The block was considered failed if any one of the four nerve territories was spared or any local anaesthetic supplementation or IV analgesics were required intra-operatively and such patients were planned to be excluded from the study.

Onset and duration of sensory and motor block and duration of analgesia were studied as primary outcome and hemodynamic parameters and sedation scores were studied as secondary outcome.

A pilot study was conducted with five patients in each group with which sample size was calculated using duration of analgesia as the primary end point. To find out a clinically significant difference of 60 minutes at a significance level of 0.05 and a power of 80%, a minimum number of 14 patients were needed in each group. Considering the possibility of block failure we took 30 patients in each group. Five patients were excluded from study due to failed block- three patients from LS group and one patient each from LD30 and LD60 group. Data was compiled and analysed using Statistical Package for Social Sciences version 17.0. ANOVA test was used to compare demographic parameters like age and weight and also for comparing onset and duration of sensory and motor blockade, duration of analgesia, blood pressure and heart rate. Chi-square test was used to compare gender and sedation score. Scheffe's multiple comparison test was used for pair wise comparison of data.

Results

All the four groups were comparable regarding age, weight, sex and baseline SBP, DBP, HR and SpO₂ [Table 1]. Compared to LS group, LD₃₀ group showed no significant change in onset and duration of both

sensory and motor blockade. There was a significant prolongation in the duration of analgesia.[Table 2] No

change in sedation score was noted compared to LS group.[Table 3]

Table 1: Comparison of demographic data and base line hemodynamic parameters

Variables	LS	LD100	LD60	LD30	P value
Age(years)	37.3±10.3	38.2±11.3	35.9±8.9	34.4±8.2	0.459
Weight(kg)	63.6±7.8	66.3±10	67.3±9.8	65.2±7.6	0.449
Male: Female Ratio	16:11	19:11	16:13	18:11	0.924
Baseline SBP(mmHg)	125.6±7.9	121.1±6.9	123.6±8.9	122.9±8.7	0.236
Baseline DBP(mmHg)	80±6.2	80.1±5.6	78.2±7.2	79.7±6.4	0.640
Baseline HR(bpm)	75.9±4.8	73.9±3.4	77.9±9.1	76.0±6.3	0.123

Age, weight, baseline SBP, DBP, and HR were expressed as Mean±Standard Deviation. Male: Female ratio expressed as number of males and females in each group

Table 2: Comparison of block parameters in the four groups

Variables	LS	LD100	LD60	LD30	P value
Onset of sensory block(min)	19.5±2.9	9.3±1.0	15.5±2.2	19.3±3.3	0.000*
Duration of sensory block (min)	532.6±52.2	920.9±36.9	748.4±57.2	539.8±48.2	0.000*
Onset of motor block (min)	24.7±3.1	12.4±1.2	16.7±2.4	23.9±3.1	0.000*
Duration of motor block (min)	554.3±49.0	943.5±34.5	780.7±53.5	560.9±51.3	0.000*
Duration of analgesia (min)	579.3±53.9	980.7±46.0	816.7±55.6	637.2±57.0	0.000*

Expressed as Mean± Standard Deviation

*:- significant at 0.01 level

Table 3: Comparison of sedation scores

Sedation Scores	LS	LD30	LD60	LD100	$\chi^2=89.32$ P= 0.000*
1	3(11.1%)	8(27.6%)	3(10.3%)	0	
2	24(88.9%)	21(72.4%)	22(75.9%)	3(10%)	
3	0	0	4(13.8%)	22(73.3%)	
4	0	0	0	5(16.7%)	

Number of patients in each group with percentage in the brackets

*:- significant at 0.01 level

In LD₆₀ group, there was a statistically significant shortening of onset time and prolongation of duration of both sensory and motor block compared to both LS and LD30 groups. Duration of analgesia was also prolonged. Increase in sedation score was noted compared to LS and LD30 groups.

LD₁₀₀ group showed statistically significant decrease in onset time and increase in duration of sensory and motor blockade and prolongation of duration of analgesia compared to the other three

groups. [Table 4]. There was a significant increase in sedation score compared to all other groups.

Statistically significant decrease in SBP, DBP and HR was found in groups with dexmedetomidine [Fig. 1, 2, 3]. In LD100 group, a transient rise in both SBP and DBP was noticed during the initial ten minutes. None of the patients in any group developed hypotension. Bradycardia developed in eight patients in LD100 group, which was treated with atropine, but was not observed in other three groups. None of the patients in the whole study developed hypoxia.

Table 4: Pair wise comparison of block characteristics (Scheffe's multiple comparison test)

Variables		LS & LD30	LS & LD60	LS & LD100	LD30 & LD60	LD30 & LD100	LD60 & LD100
Onset of sensory block	F [†]	0.03	11.89	78.87	11.1	78.57	30.31
	P value	0.992	0.000*	0.000*	0.000*	0.000*	0.000*
Duration of sensory block	F [†]	0.1	90.35	297.2	87.52	297.01	60.84
	P value	0.959	0.000*	0.000*	0.000*	0.000*	0.000*
Onset of motor block	F [†]	0.54	45.33	109.77	37.27	98.31	14.13
	P value	0.653	0.000*	0.000*	0.000*	0.000*	0.000*
Duration of motor block	F [†]	0.09	105.59	312	103.21	312.67	56.6
	P value	0.966	0.000*	0.000*	0.000*	0.000*	0.000*
Duration of analgesia	F [†]	5.53	92.71	269.24	54.92	204.5	46.6
	P value	0.001*	0.000*	0.000*	0.000*	0.000*	0.000*

*: - significant at 0.01 level

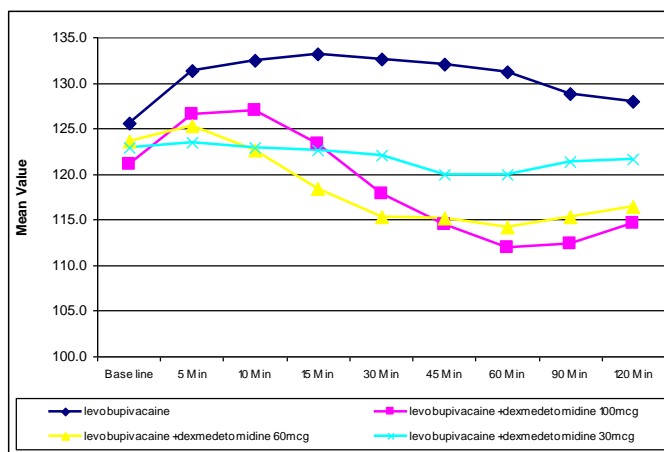


Fig. 1: Comparison of SBP among groups

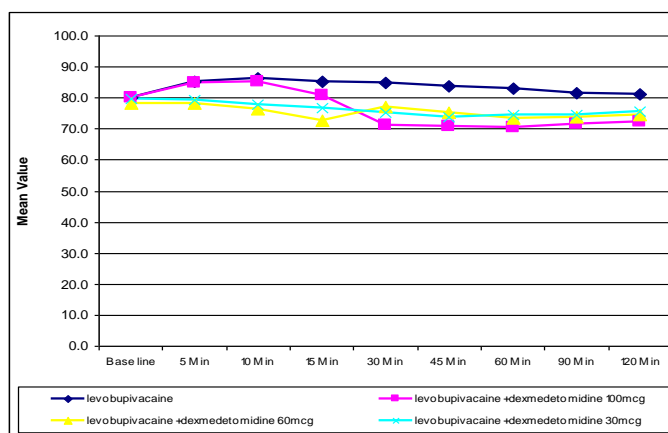


Fig. 2: Comparison of DBP among groups

Table 5: Comparison of SBP and DBP among groups (data based on which graph of Fig. 1 and Fig. 2 are drawn)

Time	LS		LD30		LD60		LD100		P value
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	
Base line	125.6±7.9	80±6.2	122.9±8.7	79.7±6.4	123.6±8.9	78.2±7.2	121.1±6.9	80.1±5.6	0.236
5 min	131.4±7.6	85.1±5.7	123.4±7.9	79.5±6.1	125.3±10.1	78.4±7	126.5±6.6	85±5.5	0.003*
10min	132.5±8.9	86.2±5.8	122.9±7.5	77.8±6.2	122.6±9.1	76.3±7.9	126.9±6.9	85.1±6.3	0.000*
15min	133.2±8.7	85.3±5.8	122.7±7.4	76.7±6.6	118.3±9.5	72.6±7.4	123.3±6.7	80.8±5.5	0.000*

30min	132.7±8.8	85±5.3	122.1±7.6	75.4±5.7	115.3±7.9	77.3±5.3	117.9±6.2	71.3±7.7	0.000*
45min	132±8.4	83.9±5.9	119.9±6.9	73.8±6.6	115.2±6.8	75.1±4.8	114.5±7.3	70.7±6.8	0.000*
60min	131.3±8.1	83.2±5.9	119.9±6.5	74.4±6.4	114.1±5.2	73.6±4.6	112±5.8	70.4±6.1	0.000*
90min	128.8±8.2	81.6±5.7	121.4±6.6	74.7±6.4	115.4±5.3	73.9±5.1	112.3±5.2	71.5±6.6	0.000*
120min	128±9	81.2±6.2	121.7±6.2	75.7±5.6	116.4±5.7	74.6±4.8	114.6±5.1	72.3±6	0.000*

*:- significant at 0.01 level

SBP and DBP measured as mmHg and expressed as mean±SD. p value for each time is given as that of SBP and DBP respectively.

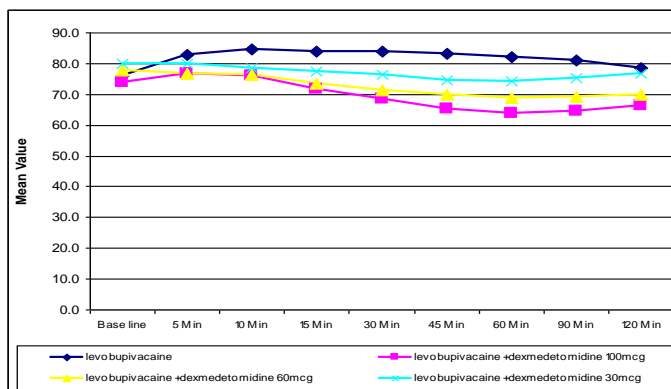


Fig. 3: Comparison of heart rate among groups

Table 6: Comparison of HR among groups (data based on which graph of Fig. 3 is drawn)

Time	LS	LD30	LD60	LD100	p value
Base line	75.9±4.8	76.0±6.3	77.9±9.1	73.9±3.4	0.123*
5 min	82.7±5.5	79.8±9.3	76.6±7.7	76.9±3.8	0.003*
10 min	84.5±5.5	78.7±8.3	76.2±7.4	75.9±5.3	0.000*
15 min	83.9±4.9	77.6±8.4	73.4±8.2	71.9±5.9	0.000*
30 min	84±5	76.4±7.8	71.3±7.8	68.4±7.1	0.000*
45 min	83.2±5.9	74.8±7.7	69.9±7.2	65.1±8	0.000*
60 min	82.2±6.2	74.4±7.1	69±6.5	63.7±9.2	0.000*
90 min	81±6.2	75.4±6.7	69±6.3	64.5±7.6	0.000*
120 min	78.7±5.7	76.8±6.9	70.1±6.5	66.2±5.9	0.000*

*:- significant at 0.01 level

HR measured in beats per minute (bpm) and expressed as Mean±SD

Discussion

Dexmedetomidine is an α_2 -adrenoreceptor agonist with excellent analgesic properties and wide margin of safety. It has α_2/α_1 binding selectivity ratio of 1620:1 as compared to 220:1 for clonidine. This high selectivity for α_2 receptors makes it more effective as a sedative and analgesic agent while minimising the unwanted effect of α_1 receptor stimulation. Agarwal et al compared equal doses (1mcg/kg) of clonidine and dexmedetomidine in peripheral nerve block and concluded that that dexmedetomidine is more efficient than clonidine in improving block characteristics.²

The mechanism by which dexmedetomidine affects the nerve block is multi-factorial. Peripherally, it acts by inhibiting the release of nor-epinephrine and also by direct effect on nerve action potential. Centrally, it acts

by activation of α_2 -adrenoreceptors of locus coeruleus and by inhibiting the release of substance P.³

Brummet et al demonstrated a dose dependent increase in sensory and motor blockade duration in rat sciatic nerve with dexmedetomidine as adjuvant to bupivacaine and found that even a very high dose of 40mcg/kg did not cause any neurotoxicity.⁴

In a study by Gandhi et al, a dose of 30mcg dexmedetomidine added to bupivacaine in supraclavicular block was found to delay the onset of sensory and motor blockade. The duration of sensory and motor blockade and duration of analgesia was found to be prolonged without any significant change in vital parameters.⁵ Marhofer et al used a smaller dose of 20mcg along with ropivacaine for ulnar nerve block in healthy volunteers and observed a faster onset of

sensory block and prolonged duration of both sensory and motor block. No significant change in onset of motor block or vital parameters was noted.³ In our study, with a dose of 30mcg, only the duration of analgesia was significantly prolonged without any effect on onset and duration of block, hemodynamic profile or sedation score. We are not able to explain the inconsistencies in block characteristics observed with lower doses of dexmedetomidine.

Almarakbi et al studied the effects of 0.5mcg/kg of dexmedetomidine along with bupivacaine in transversus abdominis plane block and concluded that perineural dexmedetomidine, in this dose, provided better pain control without any side-effects. There was no change in bi-spectral index (BIS) values as compared to control group which suggested absence of change in sedation state with a dose of 0.5mcg/kg of perineural dexmedetomidine.⁶

Rancourt et al studied the effects of 1mcg/kg dexmedetomidine along with ropivacaine on posterior tibial nerve of healthy volunteers and found a prolonged duration of sensory block with a significant fall in systolic and diastolic BP. No significant change in onset time was noted.⁷ In our study, with a similar dose of 60mcg, we got significant decrease in onset time of both sensory and motor blockade.

Lin et al studied the effects of 1mcg/kg of dexmedetomidine in cervical plexus block along with ropivacaine and found this dose significantly decreased the onset time of block, prolonged the duration of analgesia and increased the sedation score. The MAP and HR levels were significantly low from five minutes and two patients needed intervention for bradycardia.⁸

In a randomised controlled trial by Kwon Y et al, a dose of 1mcg/kg of dexmedetomidine used as adjuvant to ropivacaine in brachial plexus block caused significant improvement in block characteristics with significant decrease in HR and MAP. Of this, only one patient needed intervention for bradycardia. BIS values were decreased to around 60, which indicated a state of moderate to deep sedation from which patients were easily awakened by mild stimuli.⁹ Our results with a dose of 60mcg were consistent with that of the above study and the studies conducted by Kaygusuz et al and Obayah et al in which 1mcg/kg dexmedetomidine was used as adjuvant in axillary brachial plexus and greater palatine nerve blocks respectively.^{10,11}

In the study conducted by Yu Zhang et al using ropivacaine for axillary nerve block, addition of 100 mcg dexmedetomidine prolonged both sensory and motor blockade duration with increased incidence of hypertension, hypotension and bradycardia which needed intervention.¹² In our study also, 100 mcg dexmedetomidine showed a transient rise in BP initially followed by decrease in both HR and BP. This can be explained by the biphasic response to high dose (1-4 mcg/kg) of dexmedetomidine due to initial stimulation of α_2B receptors of vascular smooth muscles.¹³

Esmaglou et al evaluated the effect of 100 mcg dexmedetomidine added to levobupivacaine for axillary block and found that even though the block characteristics were improved, dexmedetomidine caused significant fall in HR and BP with bradycardia that needed intervention.¹⁴ Agarwal et al used 100 mcg dexmedetomidine along with bupivacaine for supraclavicular block and found a significant improvement in block characteristics including onset time and duration.² A significant fall in systolic and diastolic BP and heart rate was found, of which one patient required intervention for bradycardia. Similar results were obtained by Bisaws et al when 100mcg dexmedetomidine was used as adjuvant to levobupivacaine in supraclavicular block.¹⁵ The results we got with the same dose were consistent with that of above studies. On the contrary, Das et al reported that 100mcg dexmedetomidine used as adjuvant to ropivacaine in supraclavicular brachial plexus block prolonged the duration of block with significant decrease in heart rate without any clinically significant change in onset time.¹⁶

From our study and from previous studies with perineural dexmedetomidine, we found that higher the dose of dexmedetomidine, more improved was the block characteristics with more sedation and hemodynamic changes.

Limitations of study

1. We were not able to perform nerve blocks under ultrasound guidance due to unavailability of the same. Performing nerve blocks under USG guidance would have influenced the onset and duration of nerve blocks.
2. Our study was conducted only in otherwise healthy patients. The effects of dexmedetomidine in patients with renal, hepatic or cardiac compromise cannot be concluded from our study.
3. Monitoring BIS value would have provided objective evaluation of sedation state compared to clinical scoring systems.

Conclusion

In this double blinded comparative study, we compared the clinical profile of varying doses of dexmedetomidine as adjuvant to levobupivacaine in supraclavicular brachial plexus block. We found that the dose of 30 mcg of dexmedetomidine showed significant improvement only in duration of analgesia. Both the 60 mcg and 100 mcg doses made the onset faster and prolonged the duration of block and analgesia. Even though the dose of 100 mcg of dexmedetomidine caused a significant improvement in the block characteristics compared to 60 mcg, this advantage was offset by increased incidence of bradycardia, increased sedation and undesirable prolongation of motor block.

Thus we conclude that dexmedetomidine when used in a dose of 60mcg or approximately 1mcg/kg, as adjuvant in peripheral nerve block, has the advantages of conscious sedation, hemodynamic stability and minimal motor blockade in addition to significant improvement in block characteristics.

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