Original Article

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Effect of Fentanyl and Dexmedetomidine as Additives to 0.5% Ropivacaine in Ultrasound Guided Supraclavicular Brachial Plexus Block for Elective Upper Limb Surgeries: A Randomised Clinical Trial

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ABSTRACT

Introduction: Supraclavicular brachial plexus block is a superior alternative to general anaesthesia for upper limb surgeries, and use of ultrasound makes it safe and efficient in implementation. Ropivacaine, having significantly higher threshold for cardiotoxicity and neurotoxicity and more potent blocker of A and C fibres, renders good sensory blockade and lesser motor. Hence, to overcome this, additives are added.

Aim: To evaluate the block characteristics with addition of either fentanyl or dexmedetomidine to 0.5% ropivacaine for supraclavicular brachial block.

Materials and Methods: This randomised double-blinded clinical trial, was conducted on 50 patients posted for upper limb surgeries under supraclavicular brachial plexus block were randomly allocated to either receive 30 mL of 0.5% ropivacaine with 50 µg fentanyl (Group RF) or 30 mL of 0.5% ropivacaine with 50 µg dexmedetomidine (Group RD). The time for onset of sensory block and motor block were noted. Intraoperative haemodynamic were monitored in all the patients. Postoperatively Visual Analog Scale (VAS) scoring for pain, the time for rescue analgesia and the duration of sensory and motor blockade were noted.

Results: Both groups were comparable with respect to age, gender and American Society of Anaesthesiologists (ASA) grading. The onset of both sensory (p-value 0.008) and motor block (p-value 0.0005) was faster in Group RD compared to Group RF which was highly significant statistically. The duration of sensory (p-value 0.0005) and motor block (p-value 0.0005) was longer in Group RD compared to Group RF which was highly significant statistically. The requirement for rescue analgesia was lesser in Group RD since the mean VAS score was persistently low which was statistically significant (p-value <0.01) compared to Group RF.

Conclusion: The blockade improved better with addition of dexmedetomidine than fentanyl to 0.5% ropivacaine. There were no increased incidence for side-effects.

Keywords: Haemodynamics, Motor block, Side-effects

INTRODUCTION

Brachial plexus block is achieved commonly via interscalene, supraclavicular, infraclavicular, or axillary approach. Out of which, supraclavicular block is considered as "spinal of the arm" as it can anaesthetise the entire arm just distal to the shoulder. The use of ultrasound for supraclavicular brachial plexus block has improved the success rate of the block, as it decreases the incidence of pneumothorax and local anaesthetic systemic toxicity [1]. Regional anaesthesia has several advantages like excellent peri-operative analgesia, avoidance of airway instrumentation, avoidance of opioid-related side-effects, decreased recovery time and improved patient satisfaction [2]. Regional anaesthesia techniques have been limited by three major factors like local anaesthetic agent's slow onset time, short duration of action and limited duration of postoperative analgesia.

Short acting and long acting local anaesthetic have been combined together to have a shorter onset of action and longer duration of action. Also, several adjuvants have been used with local anaesthetics during blocks. Alpha-2 agonists like clonidine, dexmedetomidine, opioids like fentanyl, tramadol and steroids like dexamethasone have been used to prolong neural blockade [3]. Various studies have concluded that the addition of perineural dexmedetomidine to local anaesthetics significantly shortened the onset of sensory and motor block, prolongs the duration of analgesia, and prolongs the time to first analgesic request with minimal side-effects [4-6]. Addition of fentanyl to local anaesthetics enhances postoperative analgesia, but the duration of this effect was very brief [7]. The present study was conducted to compare the additives dexmedetomidine and fentanyl with ropivacaine in supraclavicular brachial plexus block. The block was performed under ultrasound guidance to achieve maximum success and better block characteristics.

The primary outcome measures were the onset and time to complete sensory and motor block and the total duration of postoperative analgesia. Secondary objectives were the haemodynamic changes following the block, sedation (Ramsay sedation score), and any side-effects of drugs used or complications related to block between the two groups.

MATERIALS AND METHODS

This randomised double-blinded clinical trial, was conducted between January 2018 to June 2019 in the Department of Anaesthesiology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India. The Institutional Ethics Committee had provided the clearance (VIEC/2017/APP/114).

Sample size calculation: Based on the study by Cham S et al.,[4] the mean±SD of the onset of motor block of two groups was 3.06±0.25 and 3.26±0.45 minutes, respectively, considering confidence Interval of 95% and power of 80% with anticipated mean difference of 0.2 and assumed standard deviation of 0.25, the sample size was estimated employing the below-mentioned formula

$n=[2*\{Z(1-\alpha/2)+Z1-\beta\}2*\sigma^2]/d^2$

$Z_{\alpha/2}=(\alpha/2)^{th}$ quantile of normal distribution

Z_{β}=(β) thquantile of normal distribution

D=difference in means

σ^2=population variance

And the calculated sample size of each group was 25 in each group, total 50.

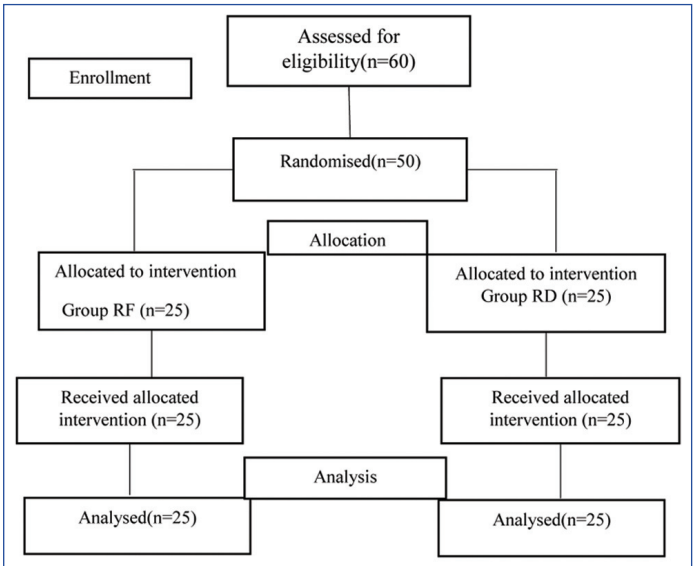
Inclusion criteria: A total of 50 patients posted for upper limb surgeries under regional anaesthesia, belonging to American Society of Anaesthesiologists (ASA) grade I and II, aged between 18 and 60 years, weighing 50-70 kgs were included in the study.

Exclusion criteria: Patients with known allergy to the study drug, those uncooperative for the block or any psychiatric illness history were excluded from the study.

The patients satisfying the inclusion criteria were thoroughly evaluated, and written informed consent was obtained. Using the sealed envelope method, patients were randomly allocated into two groups [Table/Fig-1]:

GROUP RF: 30 mL 0.5% ropivacaine+50 µg fentanyl

Group RD: 30 mL 0.5%ropivacaine+50 µg Dexmedetomidine.



[Table/Fig-1]: CONSORT flow diagram.

Study Procedure

All patients were premedicated with Injection (Inj.) Ondansetron 4 mg i.v. and Inj. midazolam 0.03 mg/kg i.v. and Inj. Glycopyrrolate 0.2 mg i.v. 30 mins before the procedure. Patients were shifted to the Operation Theatre (OT) on the day of surgery, all ASA Standard monitors attached, i.v. access secured and baseline vitals were noted. The block was performed atleast 30 minutes before the start of surgery, under sterile aseptic precautions under guidance of Seimensacuson freestyle ultrasound L8-3 MHz Linear Transducer and 22 g stimuplex needle. After completion of the injections of local anaesthetic mixture, patients were evaluated at 5 min interval for 30 mins for developing the sensory and motor block. Completion of injection was considered as time 0. Plexus block was considered successful when all the three trunks (upper, middle and lower trunks) were effectively blocked for both sensory and motor components. Surgery was started after achievement of successful blockade. In case of inadequate blockade due to any reason, the case was converted to general anaesthesia at the end of 30 minutes and it was not considered in the study.

Sensory block was assessed by pin prick test using a 3- point scale graded as

- Score 0: sharp pain;
- Score 1: touch sensation only felt; (analgesia),
- Score 2: No sensation felt; (anaesthesia). Motor block was determined by thumb abduction (radial nerve), thumb adduction (ulnar nerve), thumb opposition (median nerve), and flexion of elbow (musculocutaneous nerve) according to the modified Bromage scale on a 3-point scale as,
- Score 1: Partial block,
- Score 2: Almost complete block.
- Score 3: Total block [4]. Time of onset of sensory block, defined as the time from completion of injection to the time sensory block began to be detected in the distribution of any one of the major nerves. Time of onset of motor block, defined as the time between injection of local anaesthetic and inability to move the joints was noted. Time of complete sensory block was defined as pin prick score of 2 for all nerves. Time of complete motor block was defined as inability to move the joints or score 3. The onset and duration of sensory and motor block, time for complete sensory and motor block were noted.

Haemodynamic monitoring (heart rate, blood pressure) was noted for every 5 min till the end of the surgery. Degree of sedation was assessed at all intervals as that of vital parameter monitoring using the Ramsay Sedation Scale. Postoperatively, patients were monitored till the onset of pain and recorded as the time to first rescue analgesia. Pain was assessed by a standardised Visual Analogue Scale (VAS) every hour. The nursing staff was directed to administer first rescue analgesic Inj. Diclofenac sodium 75 mg i.v. when VAS ≥3 and second rescue analgesic Inj. Tramadol 50 mg i.v. if pain was not controlled with one analgesic drug. Any complication related to study drugs or the procedure like haematoma, pneumothorax, Horner's syndrome, recurrent laryngeal nerve palsy, bradycardia, hypotension, pruritus were noted.

STATISTICAL ANALYSIS

The data was collected in Microsoft (MS) Excel and statistical analysis was done using International Business Management (IBM). Statistical Package for Social Sciences (SPSS) statistics software 23.0 version. The results were expressed in terms of percentages and proportions and expressed in the form of tables and graphs. To describe about the data, descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean and Standard Deviation (SD) were used for continuous variables. To find the significant difference between the bivariate samples in independent groups the unpaired sample t-test and the Mann-Whitney U test was used. To find the significance in categorical data, Chi-Square test was used similarly if the expected cell frequency is less than 5 in 2×2 tables, then the Fischer's-exact test was used. In all the above statistical tools, the probability value/ p-value <0.05 was considered as significant level.

RESULTS

Total of 50 patients included in the study were analysed. There was no statistically significant difference (p-value >0.05) between the two groups with respect to age, gender and ASA grading [Table/Fig-2]. From [Table/Fig-3], it is evident that the onset of both sensory and motor block was significantly faster in Group RD compared to Group RF. The time to complete sensory block and motor block was significantly lower in Group RD compared to Group RF. The duration of sensory and motor block was significantly longer in Group RD compared to Group RF. The trends in mean heart rate depict that they remained lower than mean baseline values in both the groups [Table/Fig-4]. However, this difference in mean heart rates compared to respective preoperative mean baseline values was found to be statistically significant (p<0.01) in group RD, it was statistically significant from 25 mins interval onwards, however none of the patients had bradycardia neither in Group RD nor Group RF.

A mean MAP lower than mean baseline MAP was observed in Group RD, there was no statistically significant difference in MAP upto 60 minutes from the time of administration of block. However, the statistically significant (p-value <0.05) difference was seen from

interval of 90 mins onwards [Table/Fig-5]. Based on Ramsay sedation score, out of 25 patients in Group RD, a score of 3 was noted in 19 patients and 6 patients had a score of 2. In Group RF, all the 25 patients had a score of 1 [Table/Fig-6]. There was high statistically significant difference (p-value <0.01) in terms of sedation among Group RF and Group RD. The requirement for rescue analgesia was also lesser in Group RD since the mean VAS score was persistently low i.e. 0.2±0.58 at 10 hrs and 4.36±0.76 at 12 hrs which was statistically significant (p-value <0.01) compared to Group RF where the mean VAS score was 4.08±1.12 at 10 hrs and 4.88±0.44 at 12 hrs [Table/Fig-7]. A total of four patients in group RF requested for rescue analgesia at 6 hrs and their VAS score were high even after first rescue analgesia was given. No episode of respiratory distress or hypoxemia, Horner's syndrome, nausea, vomiting, recurrent laryngeal nerve palsy was observed in any of the patients during the study, technical complication of supraclavicular brachial plexus block administration such as haematoma formation, pneumothorax was not noted in any of patients during the study.

Variables	Group RF	Group RD	p-value
Age (in years) Mean±SD	36.6±13.5	35.0±11.6	0.647*
Gender			
Male	16	20	0.345#
Female	9	5	
ASA I/II	19/6	18/7	1.000+

[Table/Fig-2]: Demographic variables in Group RF (Fentanyl Group) and Group RD (Dexmedetomidine Group).
(*Unpaired t-test; #Mann-whitney U test; +Chi-square test); ASA: American society of anaesthesiologists

Variables in mins (mean±SD)	Group RF	Group RD	p-value (Mann-Whitney U test)
Onset of sensory block in mins	2.4±1.0	1.8±0.5	**0.008**
Onset of motor block in mins	4.7±1.5	3.0±0.6	**0.0005**
Time to complete motor block	21.7±2.6	18.1±3.5	**0.0005**
Time to complete sensory block	16.3±2.9	12.6±3.7	**0.0005**
Total duration of sensory block	490.6±65.2	623.5±63.0	**0.0005**
Total duration of motor block	471.9±74.9	601.5±63.1	**0.0005**

[Table/Fig-3]: Block characteristics between Group RF and Group RD.
bold p-values are significant

Time in minutes	HR in Group RF	HR in Group RD	p-value (Unpaired T-test)
0 min	82.920	85.160	0.465
5 min	83.800	82.880	0.774
10 min	81.160	80.560	0.825
15 min	80.360	78.320	0.431
20 min	80.080	75.440	0.073
25 min	78.440	72.640	**0.030**
30 min	78.600	70.280	**0.002**
60 min	77.880	66.240	**0.0005**
90 min	77.040	64.000	**0.0005**
120 min	77.160	63.080	**0.0005**
240 min	76.680	62.880	**0.0005**

[Table/Fig-4]: Trends in Heart Rate (HR) comparison of Group RF and RD.

Minutes	Group RF	Group RD	p-value (Unpaired T-test)
0 min	95.760	96.080	0.883
5 min	90.960	95.480	0.274
10 min	93.960	93.720	0.904
15 min	93.320	90.960	0.266
20 min	90.120	89.680	0.840
25 min	90.080	87.920	0.259
30 min	88.720	86.800	0.377
60 min	88.440	85.920	0.265
90 min	90.080	85.520	**0.036**
120 min	88.960	85.680	0.111
240 min	89.000	85.040	**0.043**

[Table/Fig-5]: MAP comparison of Group RF & Group RD.

Sedation score	Group RF count (%)	Group RD count (%)	Total	Z-value	p-value (Fischer's-exact test)
1	25 (100%)	0	25 (50%)	50.00	**0.0005**
2	0	6 (24%)	6 (12%)		
3	0	19 (76%)	19 (38%)		

[Table/Fig-6]: Comparison between Sedation Score with Groups.

Groups		Mean±SD	Z-value	p-value (Mann-Whitney U test)
VAS 2	Group RF	0	0	1.000
	Group RD	0		
VAS 4	Group RF	0.08±0.40	1	0.317
	Group RD	0		
VAS 6	Group RF	0.48±1.23	2.062	**0.039**
	Group RD	0		
VAS 8	Group RF	1.88±1.62	5.13	**0.0005**
	Group RD	0		
VAS 10	Group RF	4.08±1.12	6.32	**0.0005**
	Group RD	0.2±0.58		
VAS 12	Group RF	4.88±0.44	2.819	**0.005**
	Group RD	4.36±0.76		

[Table/Fig-7]: VAS comparison of Group RF and RD.
VAS: Visual analog scale; RF: Fentanyl group; RD: Dexmedetomidine group

DISCUSSION

The present study was carried out to compare fentanyl and dexmedetomidine as adjuvant to ropivacaine in ultrasound guided supraclavicular brachial plexus block. Ultrasound guidance produces superior peripheral nerve block success rates [1].

Ropivacaine is a long-acting amide local anaesthetic agent, is less lipophilic than bupivacaine, and is leads to a reduced motor blockade due to lesser penetration into large myelinated motor fibres. It is also associated with decreased potential for central nervous system toxicity and cardiotoxicity [8]. Increasing the concentration of ropivacaine from 0.5%-0.75% fails to improve the onset or duration of the block, while using 0.25% ropivacaine for subclavian perivascular brachial plexus block requires frequent analgesia and supplementation [9]. Adjuvants were added with ropivacaine to enhance its quality of anaesthesia in regional blocks [10]. Dexmedetomidine is a more selective α-2 adrenergic agonist and has revolutionised the field of anaesthesia [11]. Considering all this, to achieve the most effective technique and drugs for upper limb surgeries, this study used ultrasound guidance for the block with 0.5% ropivacaine and additives of dexmedetomidine 50 μg and fentanyl 50 μg.

In the present study, none of the patients were excluded from the study because of block failure. There was 100% success rate because of the use of ultrasound for block. Kathuria S et al., [5] conducted a study where dexmedetomidine was used as adjuvant to ropivacaine in ultrasound guided supraclavicular block. They also achieved good quality of anaesthesia and none of thier patients required general anaesthesia. In a landmark guided supraclavicular block conducted by Sahi P et al., [12], 7 patients were excluded from the study as there was block failure and converted to general anaesthesia.

The onset of sensory and motor blockade was lesser in the group with dexmedetomidine as adjuvant compared to fentanyl group and the postoperative analgesia was longer in the dexmedetomidine

group in the present study. Cham SC et al., [4] conducted a study using Inj. Fentanyl 1µg/kg or Inj. Dexmedetomidine 1 µg/kg as adjuvant to 30 mL of 0.5% ropivacaine, and observed that the onset of sensory and motor block was faster in dexmedetomidine group and duration of sensory and motor block and duration of analgesia was prolonged in dexmedetomidine group which was similar to the present study. Mangal V et al., [13] observed that addition of Inj. dexmedetomidine 1 µg/kg to 20 mL of 0.75% ropivacaine significantly shortened the onset of sensory and motor block in landmark guided supraclavicular brachial plexus block. Sahi P et al., [12] conducted study on landmark-guided supraclavicular plexus block with 0.5% Ropivacaine and additives of either fentanyl 1µg/kg or dexmeditomedine 1 µg/kg. Dexmedetomidine produced a more prolonged duration of motor and sensory block and postoperative analgesia as compared to fentanyl, which was significant. The mechanism of the analgesic actions of α2 agonists is multifactorial.

A number of supraspinal and spinal sites modulate the transmission of nociceptive signals in the CNS. Peripheral α2 adrenoceptors may also mediate the antinociception [5]. Kathuria S et al., compared the effect of perineural dexmedetomidine as additive to ropivacaine and intravenous dexmedetomidine. They hypothesised that it is mainly the direct peripheral action of dexmedetomidine on nerves in block, which is responsible for these improvements rather than due to central action of dexmedetomidine after absorption through block site into systemic circulation resulting in its systemic effects [5].

There were no significant haemodynamic changes in any of the study groups in the present study, however looking at the trends of heart rate in dexmedetomidine group it was noted that mean HR during the study remained lower than mean baseline HR, but none of the patients had bradycardia. Bradycardia was noticed in study patients given dexmedetomidine as adjuvant and was treated with Inj. atropine in various other studies [4,5,13]. Hypotension, nausea and vomiting was noted in few studies [4,13]. This is because of the activation of postsynaptic α-2 receptors by dexmedetomidine which leads to sympatholysis and results in decrese in blood pressure and heart rate [11]. In these studies, the dexmeditomedine dose used was either 1 µg/kg or 100 µg. Probably because the authors used a fixed lesser dose of 50µg in all patients, they didn't find bradycardia or nausea, vomiting in any of their patients.

The patients in dexmedetomidine group, in the present study, were well sedated and did not require any supplemental sedation, whereas in fentanyl group none of the patients were sedated and were given some additional sedation. Similar to the present study, sedation was seen in majority of patients where dexmedetomidine was used as adjuvant in brachial plexus block compared to the control group [12-14]. The sedative effects in dexmedetomidine group is because of systemic absorption of the drug and its action on locus ceruleus and is mediated by hyperpolarisation of noradrenergic neurons thus inhibiting noradrenaline release and inhibiting activity in descending medullospinal noradrenergic pathways [11].

Thus, with the use of appropriate technique, appropriate concentration of local anaesthetic and the additives, there was a 100% success of block, good intraoperative and postoperative analgesia with no serious side-effects. Dexmedetomidine 50 µg as additive was superior compared to fentanyl in all parameters compared in the present study.

Limitation(s)

The plasma level of the study drugs were not measured, and patients in the paediatric and geriatric age groups and patients with ASA III and above were not included in the study.

CONCLUSION(S)

Dexmedetomidine and fentanyl when used as additives to ropivacaine for brachial plexus block enhance the readiness for the surgery. Considering faster onset of both sensory and motor blockade and prolonged duration of analgesia and good quality of anaesthesia for patients with no requirement of further sedation and lack of haemodynamic instability, 50 µg dexmedetomidine is an attractive choice for supraclavicular brachial plexus block as an additive. Hence 50 µg of dexmedetomidine can safely be used as adjuvant to 30 mL of 0.5% ropivacaine without any significant side-effects.

REFERENCES

[1] Lewis SR, Price A, Walker KJ, McGrattan K, Smith AF. Ultrasound guidance for upper and lower limb blocks. Cochrane Database Syst Rev. 2015;2015(9):CD006459.
[2] Mageswaran R, Choy YC. Comparison of 0.5% ropivacaine and 0.5% levobupivacaine for infraclavicular brachial plexus block. Med J Malaysia. 2010;65(4):300-03.
[3] Dar FA, Najar MR, Jan N. Effect of addition of dexamethasone to ropivacaine in supraclavicular brachial plexus block. Indian Journal of Pain. 2013;27(3):165-69.
[4] Cham SC, Sangawar MA, Ramtani UL, Chavan BS, Cham C. Comparison of the effects of fentanyl and dexmedetomidine in supraclavicular brachial plexus block achieved with ropivacaine. Journal of Evolution of Medical and Dental Sciences. 2015;4:9427-36.
[5] Kathuria S, Gupta S, Dhawan I. Dexmedetomidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block. Saudi Journal of Anaesthesia 2015;9(2):148-54.
[6] Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anesth Analg. 2010;111(6):1548-51.
[7] Kardas K, Schools A, Concepcion M. Effect of brachial plexus fentanyl on supraclavicular block. A randomised, double-blind study. Regional Anaesthesia. 1996;20(4):311-5.
[8] Kuthiala G, Chaudhary G. Ropivacaine: A review of its pharmacology and clinical use. Indian J Anaesth. 2011;55(2):104-10.
[9] Fang G, Wan L, Mei W, Yu HH, Luo AL. The minimum effective concentration (MEC90) of ropivacaine for ultrasound- guided supraclavicular brachial plexus block. Anaesthesia 2016;71(6):700-05.
[10] Cline E, Franz D, Polley RD. Analgesia and effectiveness of levobupivacaine compared with ropivacaine in patient undergoing an axillary brachial plexus block. AANA J. 2004;72(5):339-45.
[11] Bajwa S, Kulshrestha A. Dexmedetomidine: An adjuvant making large inroads into clinical practice. Ann Med Health Sci Res. 2013;3(4):475-83.
[12] Sahi P, Kumar R, Sethi C, Gupta N, Singh A, Saxena P. Comparative evaluation of the effects of fentanyl and dexmedetomidine as an adjuvant in supraclavicular brachial plexus block achieved with ropivacaine. International Journal of Contemporary Medical Research. 2018;5(2):B25-29.
[13] Mangal V, Mistry T, Sharma G, Kazim M, Ahuja N, Kulshrestha A. Effects of dexmedetomidine as an adjuvant to ropivacaine in ultrasound-guided supraclavicular brachial plexus block: A prospective, randomised, double-blind study. J AnaesthesiolClinPharmacol. 2018;34(3):357-61.
[14] Dharmarao PS, Holyachi R. Comparative study of the efficacy of dexmedetomidine and fentanyl as adjuvants to ropivacaine in ultrasound-guided supraclavicular brachial plexus block. Turk J Anaesthesiol Reanim. 2018;46(3):208-13.

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