Original Article

Effect of dexmedetomidine on characteristics of ultrasound-guided supraclavicular brachial plexus block with levobupivacaine-A prospective double-blind randomized controlled trial

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Abstract

Background and Aims: Levobupivacaine, a less cardiotoxic s-isomer of bupivacaine, is proved to be similar to bupivacaine, hence, proposed as a safer alternative for nerve blocks. We aimed to evaluate the effect of perineural and intravenous dexmedetomidine on characteristics of ultrasound-guided supraclavicular brachial plexus block (BPB) performed with levobupivacaine. The aim of this study is to evaluate the effect of perineural and intravenous dexmedetomidine on characteristics of ultrasound-guided supraclavicular BPB performed with levobupivacaine.

Material and Methods: A prospective, randomized double-blind control trial done on 120 patients undergoing elective upper limb surgical procedures under supraclavicular BPB. The enrolled patients were allocated to one of the three groups: Group L - 0.5% levobupivacaine +0.9% normal saline (NS) IV infusion; Group LDI - 0.5% levobupivacaine + dexmedetomidine (1 mcg/kg) in NS IV infusion; and Group LDP - 0.5% levobupivacaine +1 mcg/kg of dexmedetomidine perineural + NS IV infusion. The onset and duration of sensory and motor blockade were recorded in minutes. One-way ANOVA was used to observe any differences between the groups, and post hoc comparisons were conducted after Bonferroni correction for multiple comparisons.

Results: The onset of sensory and motor blockade in Group LDP was significantly shorter than Group L and Group LDI. The duration of sensory blockade in Group LDP was significantly longer than Group LDI and Group L. The duration of motor blockade in Group LDP was prolonged compared to Group LDI and Group L.

Conclusions: When dexmedetomidine is added as adjunct to levobupivacaine in supraclavicular BPB, onset of sensory and motor blockade is faster in perineural group, whereas duration of sensory and motor blockade and duration of analgesia are more prolonged when used perineurally than intravenously.

Keywords: Dexmedetomidine, levobupivacaine, supraclavicular brachial plexus block, ultrasound-guided

Introduction

Upper limb peripheral nerve blockade has been the mainstay of anesthesiologist's interest since Hall initially reported cocaine use in brachial plexus block (BPB).[1] The interest in the field of regional anesthesia is not without a reason. Improved perioperative outcomes, increased patient satisfaction, and

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comfort as well as minimal alteration in homeostasis are some of the reasons for the growing popularity of this field.BPB at various levels has been in use for upper extremity surgeries since its description by Kulenkampff in 1928.[2] Supraclavicular approach to BPB has remained widespread because of its ubiquitous application for upper extremity surgeries, predictability, and complete anesthesia of upper limb.[3] After a brief period of disfavor owing to the risk of pneumothorax, application of nerve stimulation and the recent introduction of ultrasonography for localization of brachial plexus have rekindled anesthesiologist's interest in supraclavicular block.[4]

Although bupivacaine remains commonly used local anesthetic for performance of nerve blocks, levobupivacaine, a less cardiotoxic s- isomer of bupivacaine, is proved to be similar to bupivacaine if not for pharmaco-economic considerations, hence, proposed as a safer alternative to the former for the performance of nerve blocks.[5]Although with the increasing use of perineural catheters for pain relief, many anesthesiologists still continue to use single-shot techniques for nerve blocks. Local anesthetics with additives improve quality and the extend duration of block. Among others, selective α_2 agonist dexmedetomidine has been studied for its ability to affect the axillary BPB characteristics. Albeit availability of studies on the outcome of dexmedetomidine with levobupivacaine on axillary BPB performed by nerve stimulator guidance, no study has evaluated the consequences of intravenous and perineural dexmedetomidine with levobupivacaine on ultrasound-guided supraclavicular BPB.[6]

We studied the outcome of perineural and intravenous dexmedetomidine on characteristics of ultrasound-guided supraclavicular BPB achieved using levobupivacaine. The primary objective was to compare sensory/motor block onset and duration, duration of analgesia/first demand for rescue analgesia. Secondary objectives to look for sedation score and complications/side effects if any.

Material and Methods

This prospective, randomized double-blinded study was listed in Clinical trials registry, India {registered on: 23/03/2017 [CTRI/2017/03/008199] Trial Registered Retrospectively}. Departmental Dissertation committee and Institutional ethics committee approval were obtained before commencing this study. We included 120 patients among 18 to 60 years, ASA PS I or II, planned for elective upper limb surgical procedures (elbow, forearm, and hand) requiring supraclavicular BPB , over a period of 15 months, from 9th September 2014 to 9th December 2015 at Kasturba Hospital, Manipal. Patients with a bleeding disorder or on anticoagulants, with brachial plexus neurological deficits,

known allergy to local anesthetics, infection at block site, and history of seizures or pneumothorax were excluded. IEC approval is obtained, IEC 490/ 2014 institutional ethics committee Kasturba hospital Manipal on 09/09/2014.

All patients were evaluated on the day prior to surgery and were registered in the study after procuring informed written consent. They were kept nil per oral as per standard guidelines and premedicated as per the concerned team.

The patients were enrolled and randomly assigned to groups by a computer-generated randomization table to avoid patient selection bias. Allocation concealed using chronologically numbered opaque sealed envelopes. In Group L- Patients received (30 ml 0.5% levobupivacaine +1 ml normal saline) perineural +20 ml 0.9% normal saline IV infusion over 20 min. In Group LDI- Patients received (30 ml of 0.5% levobupivacaine +1 ml normal saline) perineural + dexmedetomidine 1 mcg/kg in 20 ml 0.9% normal saline IV infusion over 20 min. In Group LDP- Patients received (30 ml of 0.5% levobupivacaine +1 mcg/kg of dexmedetomidine in 1 ml normal saline) perineural 20 ml 0.9% normal saline IV infusion over 20 min. The IV infusion in all the groups was started immediately after the nerve block.

In the premedication area, baseline monitors attached, hemodynamic parameters, and room air oxygen saturation were noted. Intravenous access was obtained in opposite extremity, and Ringer's lactate infusion was commenced. Supraclavicular BPB was accomplished beneath aseptic precautions using 5–12 MHz linear array ultrasound probe with the patient in semi-recumbent position and cranium rolled 45° to the contralateral side. Brachial plexus was approached with a 22 G 50 mm insulated Stimuplex block needle (Braun Medical) using the in-plane method. Once the needle reaches the brachial plexus cluster, pre-decided study medication as mentioned above was injected incrementally following negative aspiration. Real-time spread of study medication at the time of injection was observed. A needle was repositioned to ensure that the drug reaches all the imaged parts of the plexus. All patients received intercostobrachial nerve block performed using a 24-gauge hypodermic needle with 5 ml of 0.25% bupivacaine.

We studied onset plus duration of sensory motor blockade. The primary outcome for our study was to find out the onset of sensory and motor blockade; the secondary outcome was to find out the duration of sensory and motor blockade along with the total duration of analgesia. Sensory blockade was evaluated with a toothpick for pinprick sensation every 3 min till the onset of loss of sensation then every 30 min till the regain of sensation in median, ulnar, radial, and

musculocutaneous nerve territories. The motor blockade was assessed every 3 min till the attainment of surgical anesthesia as defined below, then every 30 min till the complete regain of power in all four nerve territories. The contralateral upper limb was used as control. Block success was defined as the attainment of surgical anesthesia - a motor power of ≤2 according to the modified Bromage scale for upper limb, with absent pinprick sensation.[7] Block failure was described as

the nonappearance of surgical anesthesia in one or more of the four nerve territories at 30 min.

The onset of action for sensory/motor block was recorded. The time period between accomplishments of study drug deposition to loss of pinprick sensation using a toothpick in all four nerve territories (Sensory block). It was categorized as, Grade 1- Pinprick sensed; and Grade 0 - Pinprick

Table 1: Demographic data

	Group L (*n*=40)	Group LDI (*n*=40)	Group LDP (*n*=40)
Age in years (Mean±SD)	36.15±11.94	35.28±12.13	37.08±11.57
Weight in kilograms (Mean±SD)	63.13±6.42	62.68±8.34	68.13±11.59
Gender (Male/Female)	22/18	30/10	25/15
Duration of surgery in minutes	74.63±29.71	70.13±25.96	78.63±35.17

Table 2: Onset of blockade

	Group L	Group LDI	Group LDP	*P*
Sensory onset (Min) (Mean±SD)	16.58±4.02	15.98±4.26	11.55±4.93	<0.001*
Motor onset (Min) (Mean±SD)	15.68±6.57	17.70±6.47	11.10±7.69	<0.001*

*One-way ANOVA

P value<0.001: Statistically highly significant

Table 3: Duration of blockade and analgesia

	Group L	Group LDI	Group LDP	*P*
Sensory blockade (Min) (Mean±SD)	577.50±161.45	704.25±168.61	882.50±148.80	<0.001*
Motor blockade (Min) (Mean±SD)	538.88±221.09	686.25±182.82	825.75±151.71	<0.001*
Time to rescue analgesia (Min) (Mean±SD)	648.38±176.98	813.75±192.18	990.00±183.93	<0.001*

One-way ANOVA. P<0.001: Statistically highly significant. The variance of the variables was found to be homogenous between the groups, hence one-way ANOVA was used to observe any differences between the groups, and post hoc comparisons were conducted after Bonferroni correction for multiple comparisons. P<0.05 was taken as significance level
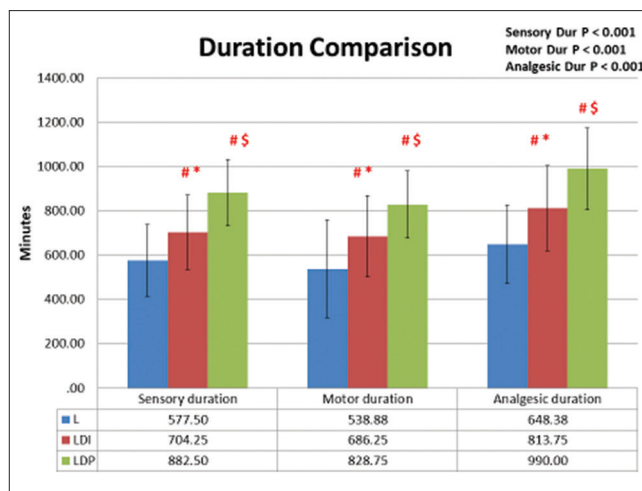
Table 4: Sedation score

	Group L	Group LDI	Group LDP	*P*
Sedation score at 1 h (Median±IQR)	2 (2-2)	3 (2-4)	3 (3-4)	<0.001#

 # Kruskal-Wallis test. P value<0.001: Statistically highly significant
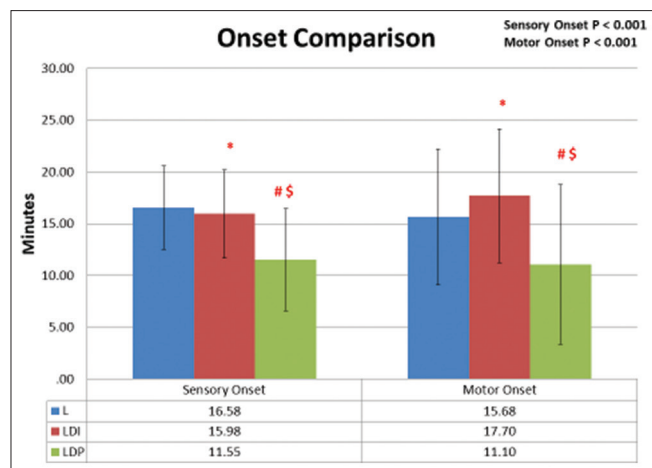
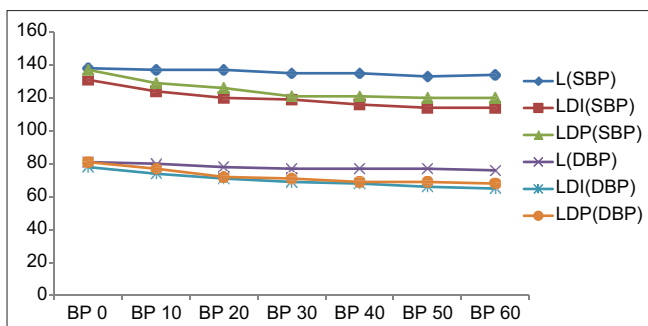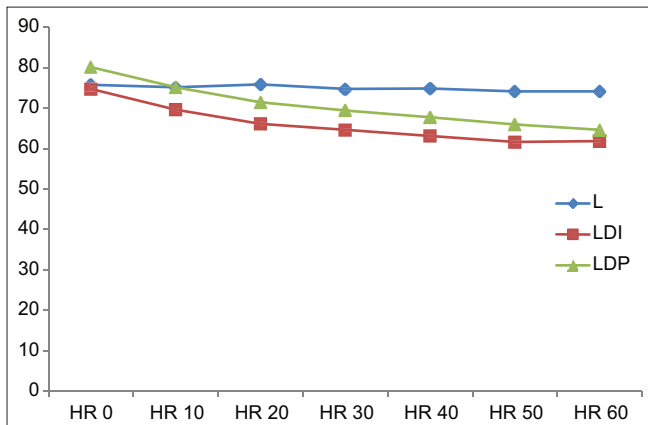**Graph 1:** Showing onset of block comparison between groups. # = Significant against Group L. $ = Significant against Group LDI. * = Significant against Group LDP
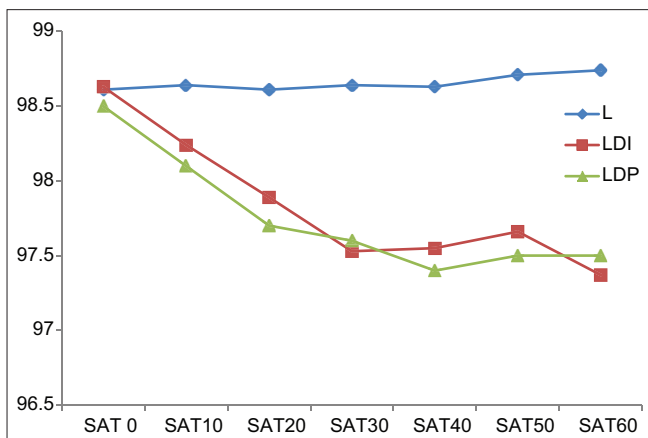

Graph 2: Showing duration of block comparison between groups

Graph 3: Blood pressure

Graph 4: Heart rate

Graph 5: Oxygen saturation

not sensed. The time interval between the completion of administration of study drug solution to a motor score of ≤ 2 as per the modified Bromage scale in all four nerve territories (Motor block). Sedation was judged by Ramsay sedation score.[8]

Duration of blockade for sensory and motor blockade was noted. The time interval between loss of pinprick sensation to the reappearance of sensation in all four nerve territories

(Sensory block). The time interval between the attainment of $\leq$ Grade 2 motor block to complete recovery of motor power in all four nerve territories (Motor block).

Unsuccessful blocks were managed with opioid supplementation, general anesthesia, and these patients were excluded from the study. If surgical procedure duration is extended and the block wears off, intravenous fentanyl 1–2 mcg/kg administered as rescue analgesia or conversation to general anesthesia.

Statistical analysis

The sample size was estimated by a pilot study, considering a 30% difference in the duration of the sensory blockade as significant, with α error of 0.05 and β error of 0.2. Minimum of 40 patients were required in each of the three groups to show 30% difference in the duration of sensory blockade, to get a power of study of 80% at 95% confidence interval.

The quantitative variables between the three groups were verified for normality of residuals using Shapiro Wilk test and found to be normally distributed with a $P > 0.01$. The variance of the variables was found to be homogenous among the groups: hence, one-way ANOVA was used to detect any variances between the groups and post hoc comparisons using Bonferroni correction for several comparisons. $P < 0.05$ was considered as significance level.

Results

Our study comprised of 120 patients, 40 patients in each Groups (Group L, LDI, and LDP). There were no dropouts in our study. The demographic profile was comparable and no statistical difference between the groups [Table 1].

The sensory onset in Group LDP (11.55 ± 4.93 min) was considerably shorter than Group L (16.58 ± 4.02 min) and Group LDI (15.98 ± 4.26 min). Similarly, motor onset in Group LDP (11.10 ± 7.69 min) was shorter than Group L (15.68 ± 6.57 min) and Group LDI (17.70 ± 6.47 min), which is statistically significant [Table 2 and Graph 1].

The duration of sensory blockade in Group LDP (882.50 ± 148.80 min) was significantly longer than Group LDI (704.25 ± 168.61 min) and Group L (577.50 ± 161.45 min). The sensory block duration in Group LDI was significantly prolonged than Group L. Similarly, the motor block duration in Group LDP (825.75 ± 151.71 min) was prolonged compared to Group LDI (686.25 ± 182.82 min) and Group L (538.88 ± 221.09 min). The duration of the motor

blockade in Group LDI was significantly lengthier than Group L. Both these parameters were clinically and statistically significant ($P < 0.001$). A similar pattern was observed when the time to rescue analgesia was compared among the three groups. Time to rescue analgesia in Group LDP was 990.00 ± 183.93 min, patients in Group LDI required rescue analgesia after 813.75 ± 192.18 min, and in Group L after 648.38 ± 176.98 min [Table 3 and Graph 2].

It was observed that patients in Group LDP and LDI had higher sedation scores at 1 h (median score: 3) than Group L (median score: 2) [Table 4].

There were no clinically and statistically significant changes in hemodynamic and oxygen saturation during and after the procedure in all the three groups [Graph 3-5].

Discussion

The attempt to conduct anesthesia in a safe and comfortable manner has been a major challenge to anesthesiologists. The benefits of regional anesthesia over general anesthesia has been well recognized, but regional anesthesia has its own set of problems. If these problems can be overcome, then regional anesthesia will be a safe and comfortable experience for the patients. Thus, anesthesiologists started probing into new avenues searching for answers.

These goals gave birth to the concept of additives with local anesthetics in regional anesthesia. The aim was to produce quick, dense, and prolonged block as well as reduce the requirement of systemic analgesics and anxiolytics. Use of additives in nerve blocks is a common practice. However, which additive to use is a dilemma considering the wide array of drugs available now. An additive which produces dense and prolonged blockade along with adequate sedation helps in avoiding the use of additional analgesics or sedatives. According to various previous studies, dexmedetomidine is an ideal drug among various additives when used in appropriate doses.

The onset of sensory blockade (In minutes) in Group L, LDI, and LDP were 16.58 ± 4.02, 15.98 ± 4.26, and 11.55 ± 4.93, respectively. The motor block onset (In minutes) in these groups were 15.68 ± 6.57, 17.70 ± 6.47 and 11.10 ± 7.69, respectively. There was an earlier onset of sensory and motor block, when dexmedetomidine added perineurally (Group LDP) as compared to dexmedetomidine added intravenously or not added to block. This finding is alike to study conducted by Esmaoglu *et al.* that sensory/motor block onset was quicker in levobupivacaine with dexmedetomidine

than plain levobupivacaine alone.[6] This difference could be owing to a higher dose of dexmedetomidine (100 mcg) used in study irrespective of body weight.

A study by Kaygusuz K *et al.* concluded that adding 1 mcg/kg dexmedetomidine in 1 ml isotonic sodium chloride to 0.5% levobupivacaine (39 ml) to axillary BPB curtails the onset of sensory block than plain levobupivacaine group and no significant difference in motor block onset.[9]

Marhofer *et al.* compared dexmedetomidine as additive with ropivacaine in ultrasound-guided ulnar nerve block, it showed no difference in sensory block onset, whereas onset of motor blockade was quicker with perineural dexmedetomidine than systemic dexmedetomidine or plain ropivacaine, but there is earlier onset of both sensory/motor blockade in LDP than LDI and L groups in our study.[10]

However, our study differs from Das *et al.* study, who noticed that dexmedetomidine supplementation to 0.5% ropivacaine in supraclavicular BPB, causes no clinically significant change in both sensory and motor block commencement.[11]

The sensory block duration in Group LDP was considerably longer than Group LDI and Group L. The sensory blockade duration in Group LDI was considerably longer than Group L. Similarly, motor block duration was prolonged in Group LDP weigh against Group LDI and Group L. The duration of motor blockade in Group LDI was significantly longer than Group L. Both these parameters were clinically and statistically significant ($P < 0.001$). A similar pattern was observed when the time to rescue analgesia was compared between the three groups. Similar prolongation of the duration of block was also observed by Esmaoglu *et al.* in their study to gagge the effect of dexmedetomidine with levobupivacaine in axillary plexus block.[6]

Our results are similar to those obtained in previous studies using dexmedetomidine as additive. The study conducted by Marhofer *et al.* using dexmedetomidine as additive with ropivacaine in ultrasound-guided ulnar nerve block showed ~60% prolongation of the block with perineural dexmedetomidine.[10] They also found a prolongation of motor block in patients who received perineural dexmedetomidine (duration of motor block = 590 ± 92 min) when matched to those who received block with plain ropivacaine (348 ± 74 min).

Sedation after the provision of the block was assessed using the sedation score described by Ramsay *et al.*[8] It was observed that

patients in Group LDP and LDI had higher sedation scores at 1 hour (median score: 3) than Group L (median score: 2). It was found to be clinically and statistically significant. These results were alike to those achieved by Agarwal *et al.*, where dexmedetomidine 100 mcg was added to 30 ml 0.325% bupivacaine, and sedation was gagged using modified Ramsay sedation score.[12] They observed that patients who received dexmedetomidine in block had higher sedation scores of 2/6 or 3/6 than plain bupivacaine (1/6).

Hall JE *et al*. reported that following administration of dexmedetomidine infusion minimal to no respiratory depression was noted, which has also been validated by the outcomes of our study.[13] The sedative effects of dexmedetomidine differ from other sedatives, as patients will remain co-operative and easily arousable.[14]

Although bradycardia with the use of dexmedetomidine was observed by Esmaoglu *et al.* in 7 out of 30 patients studied, no such events occurred during our study probably owing to the lower doses used.[6] Hemodynamic indicators (heart rate and mean arterial pressure) were stable right throughout the perioperative period, and fall in these parameters were less than 20% from baseline values among the three groups. Incidence of bradycardia and hypotension were greater in group LDI and LDP but not statistically significant.

These hemodynamic alterations were because of reduced central sympathetic outflow. Hence, we theorize that it is mainly the direct peripheral action of dexmedetomidine on nerves in the block, which is responsible for these enhancements rather than owing to dexmedetomidine central action after absorption through nerve block site into systemic circulation resulting in its systemic effects. However, the central effects of dexmedetomidine also seem to play some role in lengthening sensory and motor blockade, as 1 mcg/kg of dexmedetomidine intravenous infusion significantly prolonged BPB duration when compared to control group. However, additional studies are necessary to investigate the mechanisms of α_2 agonists, particularly dexmedetomidine, prolonging local anesthetic duration in peripheral nerve blocks.[14]

The merits of our study were that all supraclavicular BPBs were provided by a single observer using the same technique thus avoiding inter-person variation in the provision of block.

There were a few limitations to our study. The patients with variations in ultrasound anatomy of brachial plexus were also included in the study, which might have contributed to variations in onset and duration of the block. The major drawback of this study was that we could not measure plasma levels of dexmedetomidine, which possibly supported the hypothesis that dexmedetomidine has a peripheral action rather than centrally mediated.

Because of the paucity of similar studies, systemic reviews have not been done, but once we have more studies meta-analysis could be possible. Our study adds to existing findings that dexmedetomidine as adjunct improves block quality and duration, improves patient comfort. A possible mechanism should be investigated possibly with plasma levels, to determine its central or peripheral action. This was not possible in our study as our laboratory did not have the facility to measure plasma dexmedetomidine levels, and it would have added more cost to the study. Future research in this direction should be possible with measuring the plasma levels. Our study should not raise any controversy as our results match with previous studies.

To conclude, in supraclavicular BPB using ultrasound comparing, 0.5% levobupivacaine (Group L), 0.5% levobupivacaine with 1 mcg/kg dexmedetomidine infusion intravenously (Group LDI), and 0.5% levobupivacaine with 1 mcg/kg dexmedetomidine perineurally (Group LDP) showed that

1. The onset of sensory and motor blockade is faster when dexmedetomidine is added perineurally (Group LDP) as an adjunct to levobupivacaine.
2. Duration of sensory and motor block and analgesic duration are prolonged when dexmedetomidine is added as an adjunct to levobupivacaine, which is more prolonged when used perineurally (Group LDP) than intravenously (Group LDI).
3. Dexmedetomidine added either intravenously (Group LDI) or perineurally (Group LDP) causes sedation during and after the procedure.

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Conflicts of interest
There are no conflicts of interest.

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