Original Article

Comparison of the effect of intraoperative dexmedetomidine versus ketamine on postoperative analgesia in fracture femur patients operated under subarachnoid block – A prospective randomized double-blind controlled trial

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Abstract

Background and Aims: Intravenous sedation during spinal anesthesia has the advantages of increased duration of spinal anesthesia and better postoperative pain control. The aim of this study was to compare the effect of intravenous bolus and infusion of dexmedetomidine versus ketamine given intraoperative on the postoperative analgesia in fracture femur patients operated under subarachnoid block.

Material and Methods: In this prospective randomized double-blind controlled study, 75 patients aged 18–65 years posted for elective surgery were selected and randomly divided into three groups to receive ketamine (group K), dexmedetomidine (group D), and saline (control group C). Postoperative pain was evaluated using the numerical rating scale (NRS). The duration of analgesia and the amount of analgesic consumption were also recorded. Student's *t*-test and Chi-square test were used to compare the two groups, and one-way ANOVA with posthoc analysis was performed for comparison of the three groups.

Results: Patients in the ketamine group had better postoperative analgesia as assessed by decreased pain (on the NRS scale) and decreased need for postoperative rescue analgesics ($P < 0.001$). The duration of sensory block and motor block was prolonged in group K as compared to the other two groups ($P < 0.001$).

Conclusion: Intraoperative use of intravenous ketamine was superior to dexmedetomidine for postoperative analgesia in fracture femur patients operated under subarachnoid block.

Keywords: Dexmedetomidine, femur fractures, ketamine, postoperative pain, spinal anesthesia

Introduction

Though spinal anesthesia is a safe and reliable method of anesthesia for abdominal and lower limb surgery, it has an important limitation of postoperative analgesia. Pain caused by surgical procedures remains a significant clinical problem that seriously affects postoperative rehabilitation and quality of life. Recently, Fletcher *et al*.[1] reported that a 10% increase in time spent in severe postoperative pain was associated with a 30% increase in chronic pain 12 months after surgery. Chronic postsurgical pain resulting in clinically relevant functional impairment was reported by 5%–10% of the patients.[2] The magnitude of postoperative pain differs based on the type of surgery. Orthopedic surgery was associated with high incidence of chronic postsurgical pain, and preoperative pain proved to be an independent

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risk factor.[3] Multimodal analgesia is the standard of care for postoperative pain management. Multimodal analgesia emphasizes preoperative or intraoperative analgesic regimes focusing on how to prevent the development of pain sensitivity. Major analgesic drugs such as opioids, alpha2 receptor agonists, nonsteroidal anti-inflammatory drugs, N-methyl D-aspartate receptor antagonists, and local and regional anesthetics are important for pre-emptive analgesia.[4] Use of intravenous dexmedetomidine as well as ketamine when studied individually resulted in a reduction in pain score and was found to reduce postoperative pain and analgesic consumption.[5,6] However, these drugs have not been studied in patients with fractured limbs. Therefore, we planned to study the effect of these drugs on postoperative analgesia in fracture femur patients operated under subarachnoid block. Comparison of postoperative pain scores between the groups was the primary outcome. Secondary outcomes were the intraoperative level of sedation, total duration of analgesia, rescue analgesic consumption, time for sensory and motor regression, and any complications.

Material and Methods

After approval from the institutional ethics committee (EC/NIMS/2670/2020) dated 28/07/2021, the study was registered in the Clinical Trials Registry of India with the registration number CTRI/2022/05/042695, and all procedures were conducted as per the Helsinki Declaration. This trial was conducted from May 2022 to December 2022. Seventy-five patients aged 18–65 years of either gender with a fractured femur and belonging to the American Society of Anesthesiologists (ASA) physical classes I and II planned for surgery under subarachnoid block were included following consort guidelines. The study followed the principles of the Declaration of Helsinki. The exclusion criteria were patients with significant comorbidities such as ischemic heart disease, severe renal and liver impairment, patients with peripheral neuropathy, coagulation and bleeding abnormalities, patients on beta blockers, and those allergic to bupivacaine, dexmedetomidine, and ketamine. All patients were explained about the nature of the study, procedure, mode of anesthesia, postoperative pain relief that was provided, and the patient's participation in evaluating the duration of postoperative analgesia, and written informed consent was taken. All the patients were made familiarized with the numerical rating scale (NRS) in their native language.

Patients were premedicated with oral pantoprazole 40 mg and alprazolam 0.25 mg on the night before and morning of surgery. After confirming fasting status, the patients were shifted to the operation theater, and ASA standard monitors were connected. Baseline heart rate, systolic, diastolic and mean blood pressure, and oxygen saturation were noted. Intravenous access was secured in all patients. Under aseptic precautions, subarachnoid block was given in the L3–L4 space with 2.5 mL of 0.5% hyperbaric bupivacaine and 25 μg of fentanyl. Immediately after completion of the injection, the patient was made to lie supine. All patients received a balanced salt solution as the fluid of choice, and all were supplemented with oxygen at 5 $Lmin^{-1}$. After 10 min of positioning for surgery and confirmation of block, an intravenous bolus of the medication was given as per randomization and followed by infusion till the end of surgery. Vitals were recorded at every 5-min interval during surgery. Patients were allotted into three groups of 25 each by computer-generated randomization. Group D received a bolus dose of 1 μgkg^{-1} of dexmedetomidine diluted to 20 mL with normal saline (NS) slowly over 10 min. Dexmedetomidine was diluted to 4 μgmL^{-1} (200 μg in 50 mL), and an infusion dose of 0.5 $\mu gkg^{-1}h^{-1}$ was continued till the end of surgery. Group K received a bolus dose of 0.3 $mgkg^{-1}$ of ketamine diluted to 20 mL by using NS and administered slowly over 10 min. Infusion was prepared by loading the drug in a 50-mL syringe (ketamine concentration being 1.2 $mgmL^{-1}$- 60 mg in 50 mL). Infusion was given at the rate of 0.15 $mgkg^{-1}h^{-1}$ till the end of surgery. For group C (control group), a bolus of 20 mL of normal saline was given over 10 min, and infusion was given at the rate of 7.5 mLh^{-1} similar to the rate of infusion for the other two groups. One of the two anesthesiologists blinded to the study prepared the drugs and presented them as coded syringes as per randomization. Assessment and recording of intraoperative and postoperative parameters was done by an anesthesiologist who was blinded to patient allocation. The level of sedation was assessed by the Richmond agitation and sedation scale (RASS).[7] Hypotension was defined as the fall of mean arterial pressure less than 20% from baseline. This was treated with a 4 $mLkg^{-1}$ bolus of balanced salt solution. Patients not responding to fluid bolus were administered intravenous mephentermine 6-mg bolus. Bradycardia was defined as a heart rate of less than 50 and was treated with an intravenous injection of atropine 0.6 mg. Patients not responding to boluses were managed further by stopping the infusion and were excluded from the study. The number of events of hypotension, fluid boluses and amount of mephentermine administered, and number of events of bradycardia were noted. The patients who had hemodynamic instability post subarachnoid block were excluded. The patients with inadequate block or complaining in between of surgery requiring conversion to general anesthesia were also excluded from the study. Motor recovery from spinal anesthesia was assessed by modified Bromage scale.[8] Two-segment regression of sensory block was also recorded by using the pinprick method.

The postoperative outcome parameters were studied and observed to compare the efficacy of each at the following intervals: after stoppage of infusion, after shifting to the postoperative ward, and at every 4-h interval for a period of 24 h. Quantitative assessment of pain was done using NRS at the abovementioned intervals: 0 - indicating no pain, 5 – indicating moderate pain, and 10 - indicating severe pain. The first rescue analgesia was given and recorded if NRS was more than 4. The first rescue analgesic used was intravenous paracetamol, followed by intravenous diclofenac 75 mg and intravenous ketorolac 30 mg. Further regional analgesic techniques, such as femoral nerve block, were used to take care of pain if NRS >4 persistently. The total duration of analgesia was defined as the time from post subarachnoid block to the need for first rescue analgesia. The total amount of analgesics used by the patient within 24 h of operation was also recorded. Any adverse effects such as nausea, vomiting, shivering, pruritis, respiratory depression (respiratory rate <10), hallucinations, delirium, and double vision were recorded. Hemodynamic instability in the postoperative ward was managed as per standard protocol.

The sample size was based on a pilot study of a power calculation that showed that 25 patients per group were necessary to achieve 80% power and 20% differences in VAS scores between groups. Statistical package for social sciences version 20 was used for analysis. $P \leq 0.05$ was considered significant and $P \leq 0.001$ as highly significant. Quantitative data was represented by mean ± standard deviation. Student's *t*-test and Chi-square test were used as appropriate to compare the two groups. One-way analysis of variance was used to test the difference between groups after assessing the normality of data. To find out the mean values of which of the two groups have significant differences, posthoc analysis using the Tukey test was done.

Results

Out of 100 patients selected, 75 were randomized and analyzed for the study (n = 25 in each group) [Figure 1]. There was no statistically significant difference in the demographic data such as age, gender, weight, height, and body mass index (BMI) between the groups [Table 1]. There was a statistically significant difference in NRS scores between the study groups, with lower scores in group K. NRS score was higher in control at 1, 4, 8, 12, 16, and 20 h when compared to groups D and K. NRS score was lower in group K when compared to group D at 8, 12, and 16 h [Figure 2]. There was no statistically significant difference at the time of stopping the infusion and at the time of shifting to the postoperative ward. NRS score at 24 h was similar in all three study groups. There was a statistically significant difference in the need for rescue analgesics between the study groups. The total analgesic requirement in 24 h was higher in the control ($P < 0.003$) and least in the ketamine group. All the patients required 3 g of paracetamol. All the patients in group C, 56% of patients in group D (n = 14) and 32% of patients in group K (n = 8) required diclofenac 75 mg. Approximately 64% of patients in group C (n = 16), 44% of patients in group D (n = 11), and 12% of patients in group K (n = 12) required ketorolac 30 mg. None of the patients required femoral nerve block. There was a statistically significant difference ($P < 0.001$) in the duration of analgesia between the study groups. The duration of analgesia was significantly prolonged in group K (301.6 ± 28.82 min) when compared to control (181 ± 24.87 min) and group D (237.4 ± 34.27 min) [Figure 3]. The mean RASS score was significantly lower in group K (mean score of − 1.3) when compared to control and group D at all-time intervals, but the patients were easily arousable ($P < 0.001$) [Figure 4]. The duration of sensory block was prolonged in group K (204 ± 46.99 min) when compared to the control group (142 ± 29.9 min) and group D (181 ± 43.23 min), and the duration of motor block was also prolonged in group K (234.40 ± 46.82 min) when compared to the control group (157.40 ± 24.88 min) and group D (216.40 ± 33.27 min) ($P < 0.001$) [Table 2]. There were no statistically significant difference in the hemodynamics with respect to heart rate and systolic and diastolic blood pressure in all groups, and no other complications were recorded.

Discussion

In this prospective randomized controlled study, we compared the effectiveness of intraoperative infusion of dexmedetomidine

Table 1: Demographic data

Variables	Control	Group D	Group K	*P*
Age (Year) Mean±SD	47.2±14.28	44.2±13.07	45.6±16.33	0.763
Gender (M/F) (%)	72/28	72/28	76/24	0.934
Height (cm) Mean (SD)	166.2±8.332	163.7±6.420	165.9±7.282	0.438
Weight (kg) Mean (SD)	68.5±5.067	67.6±6.325	69.3±7.307	0.615
BMI (kgm^{-2}) Mean (SD)	24.7±2.4	25.5±1.98	25.2±2.33	0.445

Statistical test used – Chi-square test, M-Male, F-Female, SD-Standard deviation

Table 2: Sensory and motor block characteristics

Parameters	Group K (*n*=25)	Group D (*n*=25)	Control (*n*=25)	*P*
Duration of sensory block (min)	204±46.99	181±43.23	14±29.9	<0.001*
Two-segment regression of sensory block (min)	150.4±36.34	151.6±28.67	144.4±30.01	0.694
Duration of motor block (min)	234.4±46.82	216±33.27	157.4±24.88	<0.001*

Statistical test used- One-way analysis of variance (ANOVA)

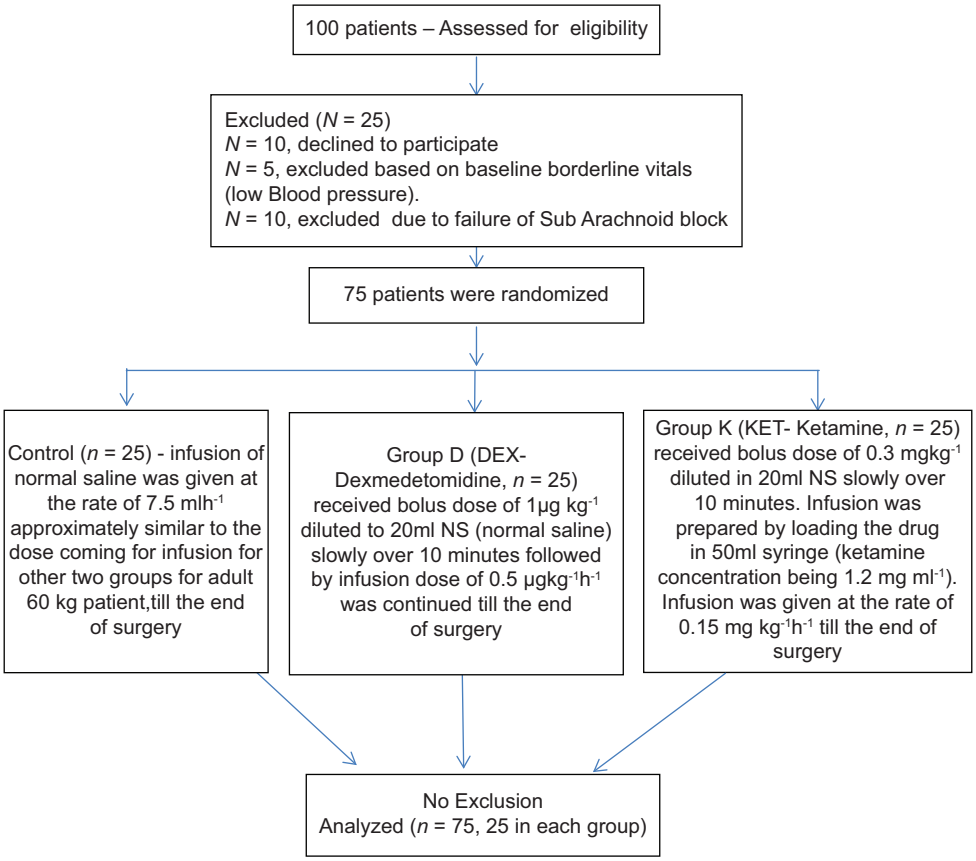

Figure 1: Consort flowchart of patients

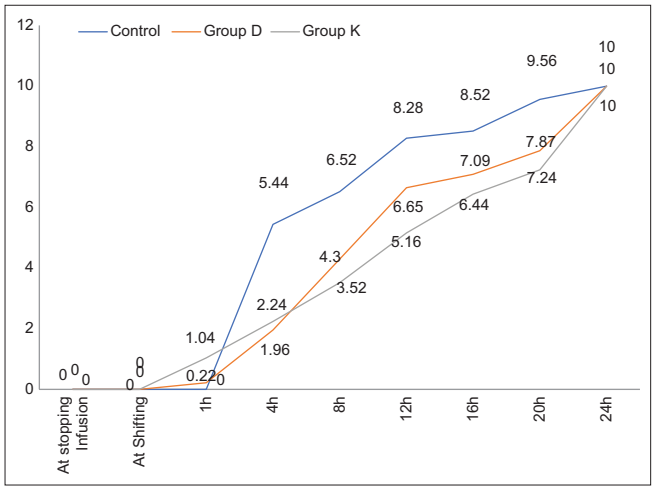

Figure 2: Comparison of mean numerical rating scale scores at different time intervals between the study groups

and ketamine for postoperative analgesia in fractured-femur patients operated under subarachnoid block. Postoperative pain management is an important aspect along with on-table patient comfort. Spinal anesthesia with adjuvants added to it has postoperative pain control and prolongs the regression of sensory and motor block, but it is associated with post-spinal bradycardia and hypotension. Thus, we need to have various modalities for better pain control and minimal effect on hemodynamics. With this understanding, we started intravenous use of the drug after adequate time of spinal anesthesia. The intraoperative infusion of dexmedetomidine and ketamine has been studied for postoperative analgesia for cases done under general anesthesia,[6,9] but its usefulness for fracture femur cases done under subarachnoid block is not well established.

There was a statistically significant difference in NRS scores between the study groups with lower scores in the ketamine group. There was no statistically significant difference at the time of stopping the infusion and at the time of shifting to

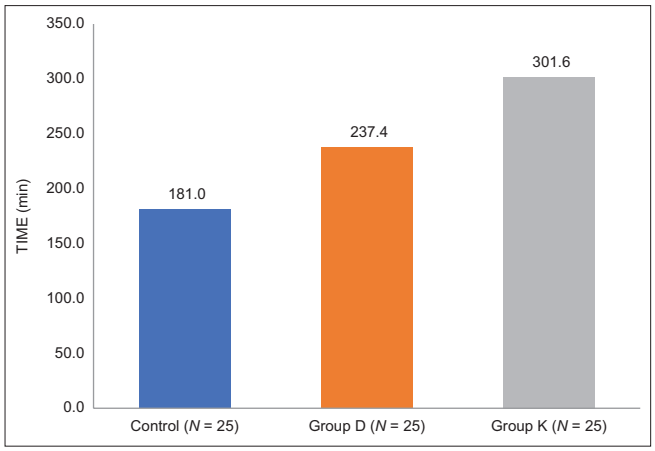

Figure 3: Comparison of the mean duration of analgesia between the study groups

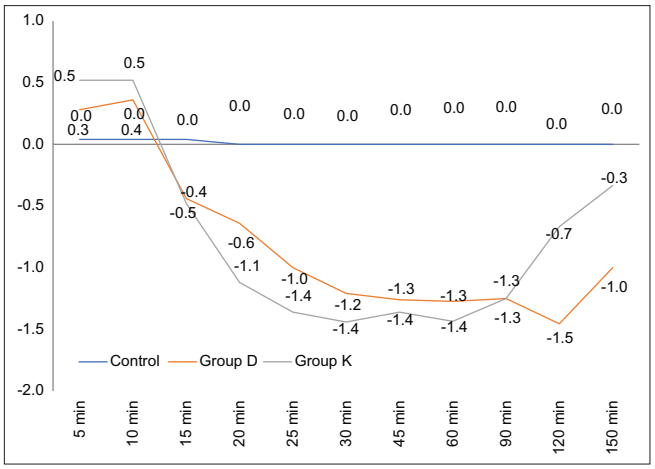

Figure 4: Comparison of mean Richmond agitation sedation scores at different time intervals between the study groups

the postoperative ward. NRS score was higher in control at 1, 4, 8, 12, 16, and 20 h when compared to groups D and K. NRS score was lower in group K when compared to group D at 8, 12, and 16 h. Ketamine has been used to manage acute and chronic pain, both alone and as an adjunct to opiates. The primary analgesic activity is through N-methyl D-aspartate (NMDA) receptor antagonism and also through action on opioid, nicotinic, and muscarinic receptors. Ketamine's anti-inflammatory qualities may also contribute to its efficacy in pain relief. Ketamine's effect on acute pain is driven by the inhibition of NMDA receptors, prevention of wind-up, and anti-depressant effect. It is also useful for treating different types of pain such as phantom limb pain. Fracture or prosthesis placement are risk factors for such types of pain, and ketamine through desensitization of up-regulated NMDA receptors and anti-depressant action may be useful to prevent this.[10-12] This may be the reason ketamine was more effective in prolonging the duration of analgesia as compared to dexmedetomidine, though both were effective. Rahmanian M *et al*.[13] conducted a study on 60 pregnant patients and found that administration of low doses of ketamine after spinal anesthesia reduces the need for analgesics and has fewer side effects than using opioids. Loftus RW *et al*.[14] conducted a study involving opiate dependent patients undergoing major spine surgery with 0.5 $mgkg^{-1}$ intravenous ketamine on induction and continuous infusion of 10 $\mu gkg^{-1}min^{-1}$ till the end of surgery. Total morphine consumption was significantly reduced in the treatment group 48 h after the procedure. In our study, dexmedetomidine was effective over the control group in terms of postoperative pain relief similar to previous studies,[15,16] but ketamine was found superior to dexmedetomidine for postoperative analgesia. Several newer studies have been done using a combination of dexmedetomidine and ketamine, showing benefits such as better hemodynamic stability, decreased respiratory depression, and reduced need for postoperative analgesia.[17] Efe Mercanoglu *et al*.[18] conducted a study to compare the effects of dexmedetomidine (0.5 $\mu gkg^{-1}h^{-1}$) or ketamine (10 μgkg^{-1} min^{-1}) administration to total intravenous anesthesia (TIVA) on postoperative analgesia in subjects undergoing elective laparoscopic cholecystectomy and found that pain scores were lower in ketamine group and dexmedetomidine group than in the control group during the 48-h period of observation. Intravenous morphine consumption was higher in the dexmedetomidine group when compared to the ketamine group. Khalil *et al*.[19] conducted a study on the perioperative use of ketamine infusion versus dexmedetomidine infusion for analgesia in obese patients undergoing bariatric surgery and found that dexmedetomidine decreased the need for intraoperative fentanyl requirement and reduced time to extubation, whereas ketamine decreased the need for morphine and had lower NRS scores.

There was a significantly lower RASS score (score of -2 to -1) in the ketamine group when compared to the dexmedetomidine group (score of 0 to − 1). There was no respiratory depression, and they were easily arousable. Similarly, Menkiti ID *et al*.[20] used 0.15 $mgkg^{-1}$ infusion of ketamine and found that 9% of patients had mild sedation. Ebong EJ *et al*.[21] used 0.25 $mgkg^{-1}$ of ketamine and reported a maximum Ramsay sedation score of 2 in the ketamine group, probably caused by the central nervous system depressant effect of ketamine. The dose used in our study is a safe dose as found in a previous study.[22]

The duration of sensory block was longer in group K (204.0 ± 46.9 min) when compared to group D (181.2 ± 43.2 min) and control (142.4 ± 29.9 min). The duration of motor block was prolonged in group K (234.4 ± 44.6 min) when compared to control (157.4 ± 24.8 min) and group D (216.4 ± 33.2 min). Ketamine has a synergistic effect with intrathecal bupivacaine,

and in previous studies, it has been shown to have delayed sensory and motor regression by both dexmedetomidine and ketamine. We also obtained similar results consistent with previous studies.[23] Cagla Ozbakis *et al*.[24] conducted a study with the addition of a small dose of ketamine (0.15 $mgkg^{-1}$) with midazolam (0.01 $mgkg^{-1}$) in 60 patients undergoing arthroscopic knee surgery under spinal anesthesia and found that sensory block and two-segment regression were significantly higher.

The range of doses and types of local anesthetics used for spinal anesthesia as well as the doses of intravenous dexmedetomidine may also affect the results. Initial loading doses of dexmedetomidine varied between 0.5 and 1 μgkg^{-1}. Most trials also included a maintenance dexmedetomidine infusion, with rates between 0.2 and 0.5 $\mu gkg^{-1}h^{-1}$, over a duration of 50 min to the entire length of surgery.[25,26] Dexmedetomidine-related side effects were higher in patients receiving larger doses. The incidence of bradycardia and incidence of hypotension showed a 1.29-fold increase when compared to the control group. These adverse effects are easily treatable.[26] In our study, none of the patients had the abovementioned complications.

In most of the published studies, effective intraoperative bolus doses of ketamine range from 0.15 to 0.5 $mgkg^{-1}$, and infusions are most commonly in the range of 0.1–0.2 $mgkg^{-1}h^{-1}$.[22] Psychosensory effects increase at doses above 0.3 $mgkg^{-1}$; thus, this can be considered an upper limit for bolus doses in awake patients.[27] In our study, none of the patients complained of hallucinations or delirium

Though this is a randomized study and blinding was done, it has a few limitations such as the perception of pain is different in different individuals, and it is difficult to standardize this subjective feeling. In this study, NRS was used to assess pain. In addition, there could be a variation in pain experienced by the patients in this study as it included all femur fractures. The effect of comorbidities was not studied as diabetes has an important correlation with postoperative pain.

Based on our observations, we can conclude that both intravenous dexmedetomidine and ketamine can be considered safe and effective methods of pain management in fractured-femur patients operated under subarachnoid block. Intraoperative use of intravenous ketamine was superior to dexmedetomidine for postoperative analgesia in fractured-femur patients operated under subarachnoid block.

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Conflicts of interest
There are no conflicts of interest.

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