

A Comparison between Intrathecal Nalbuphine versus Fentanyl as an Adjuvant with 0.5% Hyperbaric Bupivacaine for Postoperative Analgesia in Parturients Undergoing Lower Segment Cesarean Section

Abstract

Background: Nalbuphine when used as an adjuvant to hyperbaric bupivacaine has improved the quality of perioperative analgesia. Fentanyl is a lipophilic opioid with a rapid onset and does not cause respiratory depression and improves duration of sensory anesthesia without producing significant side effects. The aim of this study was to compare intrathecal nalbuphine and fentanyl as adjuvants to hyperbaric bupivacaine for postoperative analgesia in lower segment cesarean section.

Methods: A total of 100 American Society of Anesthesiologists (ASA) Physical Status (PS) I and II parturients were enrolled for lower segment cesarean section. Parturients were randomly allocated into 2 groups - Group F (n = 50) received bupivacaine 0.5% (heavy) 1.6 ml (8 mg) + fentanyl 20 µg (0.4 ml) and Group N (n = 50) received bupivacaine 0.5% (heavy) 1.6 ml (8 mg) + nalbuphine 0.4 mg (0.4 ml) under subarachnoid block (total volume = 2 ml). Time of onset and duration of sensory and motor block, Visual Analog Scale (VAS) score, duration of analgesia, sedation, rescue analgesic consumption, APGAR score, hemodynamic changes and adverse effects were noted. **Results:** Onset of sensory and motor block were significantly faster in Group F while duration of sensory block was significantly longer in Group N ($P < 0.05$). Duration of analgesia was also significantly longer in Group N (214.34 ± 9.31 min) compared to Group F (195.00 ± 9.18 min) ($P < 0.001$). No significant hemodynamic changes and adverse effects were noted in both groups ($P > 0.05$). **Conclusion:** Both of these drugs can be effectively used as an adjuvant to hyperbaric 0.5% bupivacaine in subarachnoid block for parturients undergoing lower segment cesarean section.

Keywords: Bupivacaine, cesarean section, fentanyl, nalbuphine, subarachnoid block

Introduction

Lower segment cesarean sections are most commonly performed under spinal anesthesia because of its rapid onset and complete muscle relaxation. Spinal anesthesia has several advantages over general anesthesia like lesser chances of failed block, lesser drug doses, minimal neonatal depression and lesser chances of aspiration pneumonitis.^[1,2] Hyperbaric bupivacaine 0.5% is the most common local anesthetic used for spinal anesthesia for lower segment cesarean section (LSCS). Early analgesic intervention is sometimes needed if the bupivacaine is used as a sole anesthetic agent in spinal anesthesia.^[3]

Neuraxial adjuvants are used to improve or prolong analgesia and to decrease the adverse effects associated with the usual or high doses of a single local anesthetic

agent alone.^[4-6] Opioids when used with local anesthetics have synergistic effect and intensify the sensory block without increasing the sympathetic block. Opioids used as an adjuvant to local anesthetics potentiate their effects, have dose sparing effect, and thereby reducing their complications and side effects and offer hemodynamic stability. They also prolong the duration of postoperative analgesia.^[7]

Among opioids, fentanyl has rapid onset after intrathecal injection because of its lipophilic nature. Fentanyl provides good quality of anesthesia and postoperative analgesia with minimum side effects and hemodynamic stability.^[8-11] Nalbuphine is agonist at kappa receptors (analgesia and sedation) and is antagonist at mu receptors (causes less side effects)^[12,13] Hence, in comparison to intrathecal morphine there are lesser adverse

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effects like pruritus, nausea and vomiting, addiction and hemodynamic or respiratory complications with nalbuphine.^[14,15] Despite these good qualities, the usage of nalbuphine as an additive to intrathecal local anesthetics is not widespread. Very few studies had compared intrathecal nalbuphine with other opioids.^[16]

This prospective randomized double-blind study was aimed to compare the clinical efficacy of intrathecal fentanyl (20 µg) and nalbuphine (0.4 mg) used as an adjuvant to 0.5% hyperbaric bupivacaine in patients undergoing lower segment cesarean section with a primary objective of duration of analgesia and secondary objectives of onset and duration of both sensory and motor block, pain scores (VAS), total rescue analgesia consumption, sedation score, hemodynamic changes, APGAR score and adverse effects if any.

Material and Methods

After the institutional ethics committee approval (No.979/ Acad-III/MCA/2019 Dated 15/05/2019) and written informed consent, this study was carried out on 100 parturients aged 20-40 years with American Society of Anesthesiologists (ASA) physical status I and II who underwent elective uncomplicated or low risk lower segment cesarean section. Parturients who refused to participate, allergic to local anesthetic agent or study drugs, parturients with any known cardiac, renal or hepatic disease (ASA III and above), pre-existing peripheral neuropathy or neurological deficit, parturients on anticoagulants, infection at the site of lumbar puncture and body mass index >35 kg/m² were excluded from this study.

All parturients were allocated into two groups of 50 each with the help of computer generated table of random numbers and sealed envelope technique. Group F (n = 50) received intrathecal bupivacaine 0.5% (heavy) 1.6 ml (8 mg) + fentanyl 20 µg (0.4 ml) = total volume 2.0 ml and Group N (n = 50) received intrathecal bupivacaine 0.5% (heavy) 1.6 ml (8 mg) + nalbuphine 0.4 mg (0.4 ml) = total volume 2.0 ml [Figure 1].

Preanesthetic evaluation and basic laboratory investigations were done in all the parturients, and they were explained in detail about the procedure of the spinal anesthesia during the preanesthetic visit. Parturients were familiarized with the visual analog scale (VAS) (0 - No pain; 10 - Worst pain) a day before surgery.

All parturients was kept nil per oral for at least 6-8 hours before surgery. All parturients also received preoperative aspiration prophylaxis with ranitidine 50 mg intravenous (IV) and metoclopramide 10 mg IV 30 minutes prior to surgery. All parturients were transported to operation theatre (OT) in left lateral position. After arrival in the OT, an 18G IV cannula was secured followed by preloading with 500 ml Ringer Lactate (RL) solution before subarachnoid block. Routine ASA monitoring

was established simultaneously which include pulse oximetry (SpO₂), non-invasive blood pressure (NIBP) and electrocardiogram (ECG). The baseline vital parameters which include heart rate (HR), SpO₂, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded.

Under all aseptic precautions, subarachnoid block was performed in either sitting or lateral position at the level of L3-4 or L4-5 interspace by using 25G Quincke spinal needle after clear and free flow of cerebrospinal fluid. Parturients in Group F received 0.5% hyperbaric bupivacaine 8 mg (1.6 ml) + fentanyl 20 µg (0.4 ml) (total volume 2 ml) while parturients in Group N received 0.5% hyperbaric bupivacaine 8 mg (1.6 ml) + nalbuphine 0.4 mg (0.4 ml) (total volume 2 ml) in subarachnoid block as per group allocation.

The anesthesiologist who prepared the study drugs was not a part of the study. The anesthesiologist administering the study drug and observed the parturients thereafter and the parturients were blinded to the group allocation. After subarachnoid block, the parturients were placed in the supine position with a wedge under the right hip. The surgery was allowed to start after achieving the T6 level of sensory block. Supplemental oxygen was provided through oxygen mask at the rate of 4L/min.

Sensory block was assessed by pinprick method and motor block by Modified Bromage Scale. The onset of sensory blockade (defined as the time from the injection of intrathecal drug to the absence of pain at the T6 dermatome) and onset of complete motor blockade (time taken from the injection to development of Bromage Grade 3 motor block) were recorded. The duration of sensory blockade (two segment regression from highest level of sensory blockade) was also recorded in each parturients. Duration of motor blockade (time required for motor blockade to return to Bromage Grade 1 from the time of onset of motor blockade) was also noted. Sedation during surgery was assessed by the Ramsay sedation scale (RSS). Postoperatively, pain score (VAS score) was assessed hourly for first 4 h and then at 6,12,18 and 24 h. The duration of effective analgesia (time from the intrathecal injection to the first rescue analgesic requirement or VAS >3) was noted. Intramuscular diclofenac (75 mg) was administered as rescue analgesic, and total number of doses of rescue analgesics required postoperatively in 24 h period were recorded. The various hemodynamic or vital parameters (HR, SBP, DBP, MAP, SpO₂ and respiratory rate) were continuously monitored and recorded at 5, 10, 15, 20, 25 and 30 min after the injection, and subsequently every 15 min. Parturients were also assessed for various side effects such as nausea, vomiting, hypotension, bradycardia, pruritus and respiratory depression etc. Hypotension (defined as

SBP <90 mm Hg or fall in >20% of baseline SBP) was treated with intravenous fluid initially (250 ml boluses repeated twice) and intravenous ephedrine 5 mg, if required. Bradycardia (defined as HR <60) was treated with 0.6 mg of IV atropine sulfate.

Statistical analysis

A total sample size of 100 parturients ($n = 50$ in each group) was calculated using Power and sample size calculator (PS version 3.0.0.34), α error of 0.05 and power of 80% based on previous study done by Bindra *et al.*^[22] Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 21 (SPSS Inc, Chicago, USA). Level of significance was ascertained by Chi-square test, Kruskal-Wallis test and Mann-Whitney U-test. P value <0.05 was considered statistically significant and $P < 0.001$ was considered highly significant.

Results

Both groups were comparable with respect to mean age, weight, ASA physical status, and duration of surgery ($P > 0.05$) [Table 1].

The mean time of onset of sensory block was 2.88 ± 0.65 min and 3.43 ± 0.64 min in Group F and Group N respectively. The difference was statistically significant ($P < 0.001$). The mean duration of sensory block was 79.18 ± 7.80 min in Group F and 84.00 ± 7.61 min in Group N which was statistically significant between the two groups ($P = 0.002$). The mean time of onset of motor block was 5.21 ± 0.93 min and 7.23 ± 1.08 min in Group F and Group N respectively which was also statistically significant between the two groups ($P < 0.001$). The mean duration of motor block was 99.92 ± 10.35 min in Group F and 101.90 ± 5.47 min in Group N but the difference was statistically insignificant between two groups ($P = 0.234$). In Group F, the mean duration of effective analgesia was 195.00 ± 9.18 min while in Group N, it was 214.34 ± 9.31 min which was statistically significant between the two groups ($P < 0.001$) [Table 2].

In Group F, 33 parturients required 2 doses and 17 patients required 3 doses of analgesic in first 24 hours postoperative period. In Group N, 15 parturients required 1 dose and 35 parturients required 2 doses of analgesic in first 24 hours postoperative period but none of the parturients required 3 doses in Group N. There was statistically significant difference in number of doses of rescue analgesic required in 24 hours between the groups ($P < 0.001$) [Table 3].

There was statistically significant difference in RSS scores at 30 min and 60 min ($P < 0.05$). However, there was no significant difference in RSS at 90 and 120 min in two groups ($P > 0.05$) [Figure 2]. There was statistically significant difference in mean VAS scores at 1h, 2h, 3h and 12h postoperatively ($P < 0.05$) but at 4h, 6h, 18h and 24h

there was no significant difference in VAS score in both study groups ($P > 0.05$) [Figure 3].

No statistically significant difference was found in side effects or complications in two groups ($P > 0.05$) [Table 4]. Similarly, no statistically significant difference was found in APGAR score of neonates at 1 min ($P > 0.05$).

There was no statistically significant difference regarding the various hemodynamic parameters (HR, SBP, DBP and MAP) at different time intervals between the two groups ($P > 0.05$) [Figures 4 and 5].

Discussion

The combination of local anesthetics and opioids reduces the doses of both drugs with subsequent decrease in the incidences of the associated adverse effects of each one, improves the quality of anesthesia, and increases the duration

Table 1: Demographic profile

Parameters	Group F (n=50)	Group N (n=50)	P
Age (years)	24.98±2.15	24.94±1.93	0.263
ASA PS (I/II)	45/5	40/10	0.263
Duration of surgery (min)	51.84±4.94	52.24±5.04	0.689

Table 2: Sensory and motor block characteristics

	Group F (n=50)	Group N (n=50)	P
Onset of sensory block (min)	2.88±0.65	3.43±0.64	<0.001
Onset of motor block (min)	5.21±0.93	7.23±1.08	<0.001
Duration of sensory block (min)	79.18±7.80	84.00±7.61	0.002
Duration of motor block (min)	99.92±10.35	101.90±5.47	0.234
Mean duration of analgesia (min)	195.00±9.18	214.34±9.31	<0.001

Table 3: Number of doses of rescue analgesic required in 24 h

No. of doses (rescue analgesia)	Group F (n=50)		Group N (n=50)	
	n	%	n	%
1	0	0.00	15	30.00
2	33	66.00	35	70.00
3	17	34.00	0	0.00
Total	50	100.00	50	100.00
Result (P)	P<0.001 (S)			

S=Significant; NS=Non-Significant

Table 4: Adverse effects

Side Effects	Group F (n=50)		Group N (n=50)	
	n	%	n	%
Hypotension	4	8.00	3	6.00
PONV	6	12.00	7	14.00
Bradycardia	2	4.00	3	6.00
Pruritus	1	2.00	2	4.00
Result (P)	0.937 (NS)			

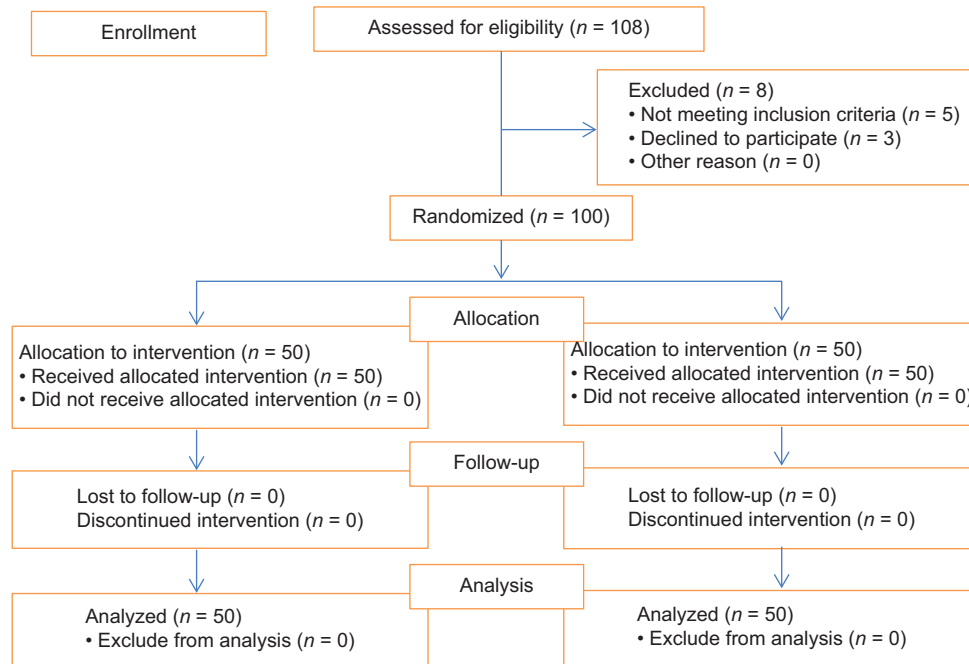


Figure 1: CONSORT flow diagram

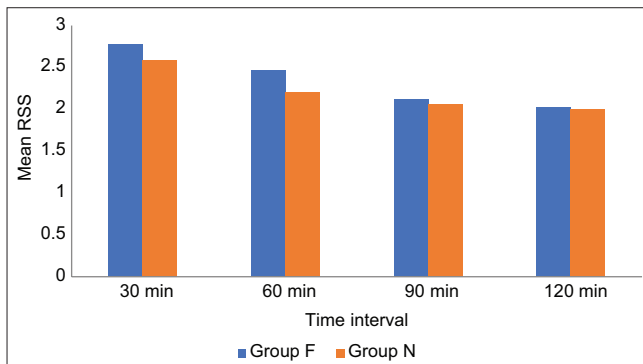


Figure 2: Modified Ramsay sedation score

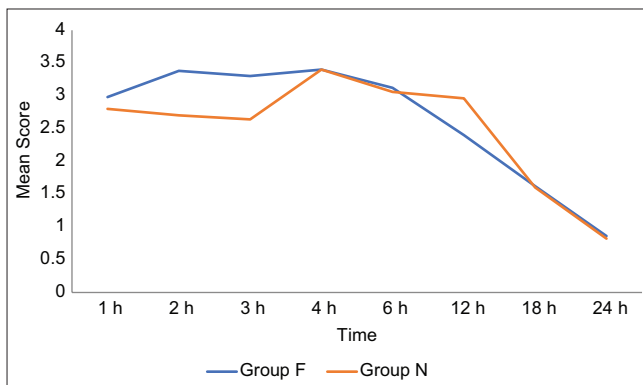


Figure 3: Postoperative visual analog scale score

of postoperative analgesia. Neuraxial opioids cause segmental analgesia and appear to act principally on μ opioid receptor in the substantia gelatinosa of the dorsal horn of spinal cord by inhibition of excitatory neuropeptide release from C-fibers.^[17] They prolong the duration of analgesia without affecting motor

or autonomic nervous function. Their combination with intrathecal local anesthetics limits the regression of the sensory block seen with local anesthetics alone.^[18,19]

Nalbuphine shows a ceiling effect to analgesia, i.e., analgesic effect increases only up to a certain point beyond which there is no further enhancement of analgesia with the increase in dose. Culebras *et al.*,^[14] Ahmed *et al.*,^[20] and Jyothi *et al.*^[21] had observed that increasing nalbuphine dose from 0.8 to 1.6 mg and 2.4 mg did not increase analgesic efficacy. According to them 0.8 mg is the best dose to improve the intraoperative analgesia and prolongs early postoperative analgesia, without increasing the risk of side effects. However, the study conducted by Tiwari *et al.*^[15] has used nalbuphine (0.4 mg) and found that 0.4 mg dose provided good intraoperative and early postoperative analgesia with minimal adverse effects and hemodynamic stability. So, we chose 0.4 mg of nalbuphine to compare with 20 μ g of fentanyl for our study.

The mean duration of analgesia was significantly prolonged in Group N as compared to Group F in our study. Our results coincide with the studies done by Bindra *et al.*^[22] and Ahmed *et al.*^[20] They showed that the mean duration of analgesia was found to be significantly higher in Group BN (225.4 ± 82.3 min) as compared to Group BF (176.1 ± 46.4 min) ($P < 0.001$). However, Vashishth *et al.*^[23] and Gupta *et al.*^[24] found that mean duration of analgesia was significantly prolonged in fentanyl group as compared to nalbuphine group which was contrary to our study findings who had used 15 mg bupivacaine in their studies in comparison to 8 mg in our study. The might be due to the fact that fentanyl probably increases the synergistic effect with increasing dose of

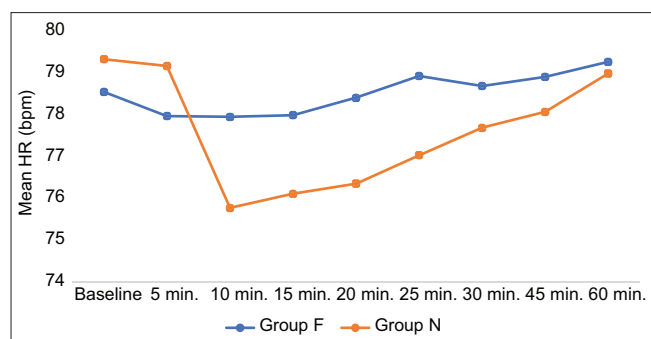


Figure 4: Mean heart rate

bupivacaine. Similarly, there was insignificant difference in mean duration of analgesia in studies by Gomma *et al.*^[25] and Ibrahim *et al.*^[26]

In present study, the onset of sensory block was significantly earlier in Group F as compared to Group N. Ahmed *et al.*,^[20] Ibrahim *et al.*^[26] and Vashishth *et al.*^[23] also showed similar results to our study. However, the results of Gupta *et al.*^[24] were contrary to our findings, where the onset of sensory block was significantly faster in nalbuphine group as compared to fentanyl group.

The duration of sensory block (two segment regression) was significantly prolonged in Group N as compared to Group F. Our study results coincide with the study done by Ahmed *et al.*,^[20] Ibrahim *et al.*^[26] and Garg *et al.*^[27] who had used fentanyl and nalbuphine as adjuvants with bupivacaine in urological procedures and found similar results. Gomma *et al.*^[25] studied similar drugs in lower segment cesarean section but they found insignificant difference in the duration of sensory block ($P > 0.05$). However, Bindra *et al.*^[22] also compared these two drugs and found that fentanyl significantly prolonged the duration of sensory block ($P = 0.035$).

Onset of motor block was earlier in Group F as compared to Group N. This parameter was also observed by Gomma *et al.*,^[25] Ahmed *et al.*^[20] and Ibrahim *et al.*^[26] whose results were similar to our study results. Bindra *et al.*,^[22] Gupta *et al.*^[24] and Garg *et al.*^[27] studied similar drugs but, no significant difference was noted in onset of motor block in their studies. Vashishth *et al.*^[23] used similar drugs in lower limb and lower abdominal surgeries but the onset of motor block was found to be faster in nalbuphine group which was contrary to our findings.

The duration of motor block was comparable in both study groups. The results of our study were coinciding with Gomma *et al.*,^[25] Ahmed *et al.*^[20] and Bindra *et al.*^[22] Gupta *et al.*^[24] and Garg *et al.*^[27] studied similar drugs for lower limb, lower abdomen and urological surgeries and they had also found similar results in terms of duration of motor block. But Ibrahim *et al.*^[26] showed significant difference in duration of motor block in nalbuphine group and fentanyl groups which was also not supported the results of our study.

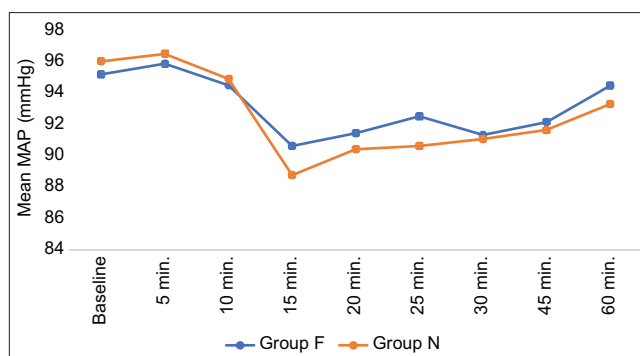


Figure 5: Mean arterial pressure

In our study, there was significant difference in the modified RSS scores in both the study groups at 30 and 60 minutes with significantly higher sedation score in Group F. However, at 90 and 120 minutes both groups were comparable with regards to sedation. Although RSS score was significantly higher in Group F at 30 and 60 minutes but it was clinically insignificant and patients remained arousable throughout the perioperative period. Our study results coincides with the findings of Bindra *et al.*^[22]

In our study a statistically significant difference was noted in mean VAS score at 1h, 2h, 3h and 12h postoperatively ($P < 0.05$). However, at 4h, 6h, 18h and 24h there was no significant difference in VAS score in both study groups ($P > 0.05$). The mean VAS score was lower in Group N as compared to Group F in early postoperative hours. The parturients in Group N required lesser amount of rescue analgesics than in Group F ($P < 0.001$). The findings of our study were comparable with Bindra *et al.*^[22]

Both groups were comparable with regard to various hemodynamic parameters. Our results are in accordance with Gomma *et al.*^[25], Ibrahim *et al.*^[26] and Bindra *et al.*^[22] who found that there was no significant difference in hemodynamic parameters between the groups. In our study, the APGAR score at 1 min was 8.40 ± 0.70 in Group F and 8.54 ± 0.503 in Group N ($P = 0.253$), which was statistically insignificant. Thus, we observed that both drugs did not adversely affect the neonatal outcome when used intrathecally. Our results were consistent with the findings of Gomma *et al.*^[25] and Ahmed *et al.*^[20]

Conclusion

From our study we concluded that both fentanyl and nalbuphine increased the duration of postoperative analgesia when used as an adjuvant to hyperbaric 0.5% bupivacaine in subarachnoid block in parturients who underwent lower segment cesarean section. Although fentanyl (20 μ g) was found to be better in terms of faster onset of both sensory and motor block but nalbuphine (0.4 mg) was found to be better in terms of both duration of sensory block and duration of postoperative analgesia along with stable

hemodynamics and minimal side effects. So, both of these drugs can be effectively used as an adjuvant to hyperbaric 0.5% bupivacaine in subarachnoid block for parturients undergoing lower segment cesarean section.

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Conflicts of interest

There are no conflicts of interest.

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