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Intravenous morphine plus ibuprofen or ketorolac versus intravenous morphine alone in reducing renal colic pain intensity in emergency department: A randomized, double-blind clinical trial

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Abstract:

OBJECTIVES: This study aimed to compare the efficacy of intravenous (IV) morphine plus ibuprofen or ketorolac versus IV morphine alone in controlling renal colic pain in the emergency department.

METHODS: This double-blind, randomized clinical trial was conducted during November 2018 and March 2019 in Iran. Patients aged 18–65 years with acute renal colic and numerical rating scale (NRS) score of higher than 6 of 10 were enrolled to the study. They were randomly assigned to I, K, and control groups receiving 5 mg morphine with 800 mg ibuprofen ($n = 65$), 5 mg morphine with 30 mg ketorolac ($n = 65$), or only 5 mg morphine ($n = 65$) intravenously, respectively. NRS was evaluated 0, 15, 30, 60, and 120 min after injection.

RESULTS: A total of 195 participants took part in the study. The presence of stone in pelvis area was higher in I group ($P = 0.027$). The mean rescue analgesic dose was higher in the control group and lower in K group ($P = 0.031$). From the 15th min, the NRS reduction in I and K group was higher than the control group ($P < 0.001$), but the difference between I and K group was not statistically significant in total ($P = 1.0$) or in the all follow-up time intervals (15th $P = 0.864$, 30th $P = 0.493$, 60th $P = 0.493$, and 120th min $P = 1.0$). The largest difference in pain reduction was observed in 120th min and mean of NRS was 2.9 (95% confidence interval [CI]: 2.6–3.3), 2.9 (95% CI: 2.6–3.3) and 7.0 (95% CI: 6.7–7.4) in I, K and control group, respectively. The adverse effects showed in 18.5%, 20.0%, and 13.8% of I, K, and control group, respectively.

CONCLUSION: IV ibuprofen plus morphine and IV ketorolac plus morphine had similar effects in reducing renal colic pain but were more effective than IV morphine alone.

Keywords:

Emergency service, hospital, ibuprofen, ketorolac, pain management, renal colic

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Box-ED section

Acute renal colic is one of the most common issues in the emergency department (ED) and choosing the best analgesics has a major and increasingly important role to abate the symptoms with the fastest and most efficient method. This study attempted to compare the effects of intravenous (IV) morphine plus ibuprofen or ketorolac versus morphine alone for pain control in patients with acute renal colic in ED.

Our study showed that IV ibuprofen plus morphine or ketorolac plus morphine had similar effects in reducing pain and were more effective than morphine alone. Both IV ketorolac plus morphine and IV ibuprofen plus morphine were better choices than IV morphine alone in controlling renal colic pain.

Introduction

Urolithiasis has a worldwide prevalence of almost 5%–15% in the general population.[1,2] Urolithiasis mostly presents as severe acute colicky pain radiating from the flanks to the groin, which is defined as the worst pain in a person's life. The pain intensity differs due to the size and location of stone and degrees of obstruction.[3-5] Acute renal colic is one of the most common complaints in the emergency department (ED), and the major concern in the health management is to abate the symptoms with the fastest and most efficient method.[6-8]

A review of 57 articles on the different therapeutic approaches for renal colic pain indicated that opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), or combination of both, especially intravenously, are the most effective options in this regard.[7] Opioid analgesics such as morphine can alleviate the renal colic pain through the central nervous system. However, some physicians prefer to use alternative agents due to possible adverse effects of opioids such as ineffectiveness to control the pain cause, opioid dependence, nausea, vomiting, sedation, disorientation, hemodynamic compromises, and respiratory depression.[7,9] Various studies recommended that NSAIDs as appropriate and effective alternatives reported lower adverse effects, alone or in combination with opioids for alleviating renal colic pain.[10,11] NSAIDs can control renal colic pain by reducing the glomerular filtration rate, renal pelvic pressure, ureteric peristalsis, edema, and inflammation.[7,12,13] The efficacy of the combination of NSAIDs and morphine in renal colic pain management is still at a matter of debate. In this regard, a study stated no significant difference in the reduction of renal colic pain among rofecoxib plus morphine and diclofenac plus morphine and morphine alone.[14] However, a study showed that the combination of morphine plus ibuprofen or ketorolac was significantly a better pain management compared to ibuprofen or ketorolac alone.[15] A review of 65 randomized clinical trials (RCTs) showed that the combination of NSAIDs and morphine was more effective in the reduction of renal colic pain at 30 min, but NSAIDS had priority to morphine and combination therapy at full consideration of all outcomes.[11]

Limited number of studies tried to compare the efficacy of NSAIDs in combination with morphine and controversies are still present. Therefore, this study was performed to compare the effects of intravenous (IV) morphine plus ibuprofen or ketorolac versus morphine alone to control pain in patients with renal colic in ED.

Methods

Study design and setting

This double-blind RCT was conducted during November 2017 and March 2018, at ED of Sina Hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran The implementation protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (code: IR. TUMS. VCR. REC.1398.844). The clinical trial was registered at Iranian Registry of Clinical Trial (code: IRCT20150213021063N5). The study was conducted in accordance with the declaration of Helsinki principles. Written informed consent was obtained from all participants prior to enrolment.

Selection of participants

All patients aged 18–65 years referred to the ED with acute renal colic pain (diagnosed based on the result of renal ultrasound clinical presentation) that had Numerical Rating Scale (NRS) of higher than 6 of 10 were eligible. Sampling was done by the convenience method. The exclusion criteria were as follows: Weight <50 kg (because of required dosage adjustment of ketorolac), pregnancy, breastfeeding, volume depletion (based on physical examination), systolic blood pressure <100 mmHg, any active bleeding, history of hypersensitivity to NSAIDs or aspirin (such as asthma attack, skin allergy, anaphylactic reaction, etc.), history of renal failure, heart failure, peptic ulcer disease, gastrointestinal bleeding, coagulation disorders, and those who received anticoagulant agents or medications interfering with platelet function. Patients who could not continue the survey were also excluded from the study.

Sample size estimation

Sample size was calculated to achieve 80% power at an alpha of 0.05 to detect a minimum clinically significant mean difference in pain severity of 1.3 points between-group with a standard deviation (SD) of 2.6 points for the NRS. Sixty-four patients should be included in each group. We calculated minimum sample size

required based-on comparison of means formula ($n = [Z\alpha/2 + Z\beta]^2 \times 2 \times \sigma^2/d^2$).

Primary assessment

Data including age, gender and history of renal stone, history of taking any analgesics during 6 h prior to ED admission, duration between the symptom onset and arrival at ED (in three categories of <6 h, 6–24 h, and more than 24 h), stone size, and location of stone were gathered in a preprepared data collection form.

The stones were located in six different places including ureterovesical junction, proximal, middle, or distal part of ureter, ureteropelvic junction, and pelvis by the reported result of nonenhanced multidetector abdominopelvic computed tomography (CT) scan.

The evaluation of pain severity for all patients was carried out based on NRS index due to its ease of use. The score ranges from 0 (no pain) to 10 (worst pain).

Randomization and blinding

Patients were randomized into three groups (ibuprofen, ketorolac, and control) by using the computer-generated allocation table provided by RANDOM. ORG website.[16] The randomized allocation table was provided to indicate which drug code should be given to the patients in a randomized manner. One of the investigators who were not involved in the data gathering and analyzing had prepared the drugs with the codes and the codes were not revealing the identity of the drug contents. Color and appearance of the drugs were identical. The drugs were administered to the patients by a nurse. Patients, nurses, and physicians were all blinded to their assessments.

Interventions

In the ibuprofen (I) group, we administered 5 mg morphine sulfate intravenously in 5 min, 800 mg of ibuprofen in 200 mL normal saline intravenously in 30 min, and 2 mL distilled water intravenously in 30 s. In the ketorolac (K) group, we administered 5 mg of morphine sulfate in 5 min, 200 mL normal saline intravenously in 30 min, and 30 mg of ketorolac (2 mL) intravenously in 30 s. In the control group, we administered 5 mg morphine sulfate intravenously in 5 min, 200 mL normal saline intravenously in 30 min, and 2 mL distilled water intravenously in 30 s. The dose of drugs was selected based on earlier studies.[10,17-19]

Outcomes

NRS was used for patients in all treatment groups 0, 15, 30, 60, and 120 min after injection. The patients were asked by an investigator about the severity of their pain and a score ranges from zero (no pain) to 10 (worst pain) give to it. If the score of NRS in the 30th min was higher than 6 of 10, then 5 mg morphine sulfate was slowly administered intravenously in 5 min and repeated if the patient's pain intensity on NRS remained more than 6 in 15 min intervals. The rescue analgesia doses for each patient were also measured. Reduction of NRS score in the 30th min was considered as primary outcome and reduction of pain in 60th and 120th min, adverse effects (including pain in injection site, respiratory depression, nausea, vomiting, and anaphylaxis or allergic reactions like erythema of injection site) until the patients discharge from the hospital, rescue analgesia doses and duration of hospitalization were considered as secondary outcomes, that all were recorded by one of the investigators.

Statistical analysis

The data were analyzed using the SPSS software version 22.0 (SPSS Inc., Chicago, Ill, USA). Before the use of the repeated measure of analysis of variation test, we assessed the normality using Kolmogorov–Smirnov and graphical approaches, the equality of covariance matrices with Box's test and sphericity assumption with Mauchly's test. The normal quantitative variables were described using mean ± SD. The nonnormal quantitative variables were described using median with interquartile range. The qualitative variables described using the frequency and percentage. The Analysis of Variance (ANOVA) test was used to compare the quantitative variables. The Chi-square or Fisher's exact test was used to compare the qualitative variables. Kruskal–Wallis test was applied on nonnormal quantitative variable including stone size. The NRS alteration in the follow-up was assessed with repeated-measures ANOVA. The *post hoc* multiple comparison was done based-on Bonferroni method. $P < 0.05$ was considered statistically significant.

Results

One hundred and ninety-five patients (55.9% male) with a mean age of 39.5 ± 12.2 years took part in the study. They were divided into three treatment groups [Figure 1]. Demographic and baseline data are shown in Table 1. There was no significant difference between treatment groups in the terms of age ($P = 0.974$) or gender ($P = 0.979$).

Of all I group participants, 21.5% have a history of urolithiasis and the median of kidney size in this group was 2.0 cm. The history of urolithiasis and size of stone were higher in I group, but the difference was not statistically significant ($P = 0.508$ and $P = 0.412$, respectively) [Table 1].

Twelve patients did not undergo CT scan for determination of the location of stone. The most and least common location of stone was the distal part of ureter (29.5%) and pelvis area (7.1%). In patients who underwent CT scan

Table 1: Clinical presentations and demographic characteristics in the treatment groups

Variables	Total (*n*=195)	Treatment groups			*P**
		Ibuprofen (*n*=65)	Ketorolac (*n*=65)	Control (*n*=65)	
Age, mean±SD	39.5±12.1	39.5±12.5	39.3±12.4	39.8±11.5	0.974
Sex; male, *n* (%)	109 (55.9)	36 (55.4)	37 (56.9)	36 (55.4)	0.979
History of urolithiasis, *n* (%)	34 (17.4)	14 (21.5)	11 (16.9)	9 (13.8)	0.508
Kidney stone size (cm), median (IQR)	2.0 (4.0)	3.0 (4.0)	1.5 (4.0)	2.0 (3.7)	0.412
Location of the stone					
Pelvis	13 (7.1)	9 (14.8)	2 (3.2)	2 (3.3)	0.027a
UPJ	31 (16.9)	11 (18.0)	10 (16.1)	10 (16.7)	0.959
Proximal ureter	29 (15.8)	11 (18.0)	8 (12.9)	10 (16.7)	0.722
Middle ureter	18 (9.8)	4 (6.6)	9 (14.5)	5 (8.3)	0.298
Distal ureter	54 (29.5)	16 (26.2)	17 (27.4)	21 (35.0)	0.518
UVJ	38 (20.8)	10 (16.4)	16 (25.8)	12 (20.0)	0.430
History of taking any analgesics six hours prior to ED admission, *n* (%)	27 (13.8)	11 (16.9)	9 (13.8)	7 (10.8)	0.597
Duration between symptom onset and arrival at ED, *n* (%) (h)					
<6	92 (47.2)	29 (44.6)	34 (52.3)	29 (44.6)	0.598
6-24	67 (34.4)	23 (35.4)	19 (29.2)	25 (38.5)	0.432
>24	36 (18.5)	13 (20.0)	12 (18.5)	11 (16.9)	0.903

*P-value refers to the relation between each variable and the treatment groups, [a]P-value refers to the relation between variables based-on Fisher's exact test. SD=Standard deviation, UPJ=Ureteropelvic junction, UVJ=Ureterovesical junction, IQR=Interquartile range, ED=Emergency department

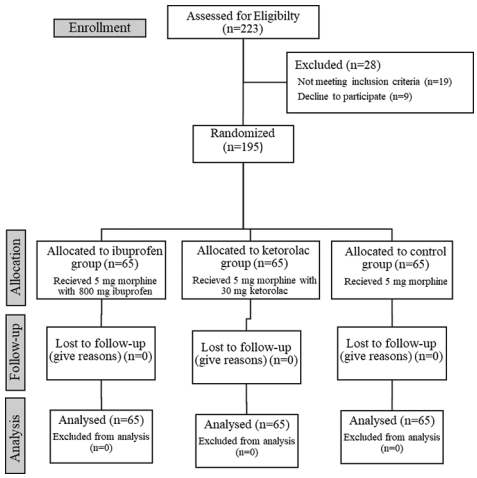

Figure 1: CONSORT flow diagram of the trial

and the frequency of stone in pelvis area was significantly higher in I group (14.8%) versus 3.2% in K group and 3.3% in control group ($P = 0.027$) [Table 1].

History of taking any analgesics 6 h between ED admission ($P = 0.597$), duration between symptom onset and arrival at ED ($P = 0.818$) had no significant difference in treatment groups [Table 1].

The longest and the shortest duration of hospitalization was in K group (2.6 h) and I group (2.2 h), respectively, but the difference was not statistically significant ($P = 0.407$) [Table 2].

The mean rescue analgesic dose of I, K, and control groups was 1.4 ± 0.48, 1.2 ± 0.36 and 2.1 ± 1.1, respectively, and ANOVA test showed that the mean rescue analgesic dose in the control group was significantly higher than K group ($P = 0.031$). However, *post hoc* test showed no significant difference on the mean dose of rescue analgesic between I group and K group ($P = 1.0$) or I group and control group ($P = 0.217$).

The mean of NRS in all three groups was 8.4 in the baseline and was not significant difference in three groups ($P = 0.994$). Evaluation of NRS index had no significant difference before the intervention but from 15th min, the reduction of pain in I and K group were significantly better than control group ($P < 0.001$). The largest difference in pain reduction was observed in 120th min and mean of NRS was 2.9 (95% confidence interval [CI]: 2.6–3.3), 2.9 (95% CI: 2.6–3.3) and 7.0 (95% CI: 6.7–7.4) in I, K, and control group, respectively.

The NRS index was significantly decreased in all treatment groups in the follow-up time interval ($P < 0.001$). The reduction rate of NRS in I and K group was significantly greater than control group ($P < 0.001$), but the difference between the reduction of NRS among I and K group was not statistically significant in total ($P = 1.0$). Furthermore, based-on *post-hoc* test for multiple comparison of three groups in the all follow-up time intervals, mean of NRS index between I and K group was not statistically significant (15th $P = 0.864$, 30th $P = 0.494$, 60th $P = 0.493$ and 120th min $P = 1.0$) [Figure 2 and Table 2].

The adverse effects showed in 18.5%, 20.0%, and 13.8% of I, K, and control group, respectively. The history of

Table 2: The outcome of studied population in the treatment groups

Variables	Total (*n*=195)	Treatment groups			*P**	*P***
		Ibuprofen (*n*=65)	Ketorolac (*n*=65)	Control (*n*=65)		
Duration of hospitalization (h), mean±SD	2.43±1.8	2.2±1.8	2.6±1.9	2.5±1.7	0.407	0.565
NRS, mean (95% CI)	Baseline	8.4 (8.2-8.6)	8.4 (8.2-8.6)	8.4 (8.2-8.6)	0.994	1.0
	15th min	7.3 (7.1-7.5) a	7.1 (6.9-7.3) a	7.9 (7.6-8.1) b	<0.001	0.864
	30th min	6.1 (5.9-6.4) a	5.9 (5.6-6.1) a	7.5 (7.2-7.8) b	<0.001	0.494
	60th min	4.8 (4.5-5.1) a	4.5 (4.2-4.8) a	7.4 (7.1-7.7) b	<0.001	0.493
	120th min	2.9 (2.6-3.3) a	2.9 (2.6-3.3) a	7.0 (6.7-7.4) b	<0.001	1.0
	P-value for follow-up	<0.001	<0.001	<0.001		
Adverse effects, *n* (%)	34 (17.4)	12 (18.5)	13 (20.0)	9 (13.8)	0.629	0.824

In numerical variables, mean differences were assessed by the ANOVA test. [a,b]Post-hoc comparison based-on Bonferroni method. Different superscript letters (a, b) in the same row of variables reflect significant (P<0.05) difference between the means while same superscript letters in one row reflect non-significant difference. *P-value refers to the relation between each variable and the treatment groups, **P-value refers to the relation between Ibuprofen and Ketorolac group based-on Bonferroni method. SD=Standard deviation, NRS=Numerical Rating Scale, CI=Confidence interval

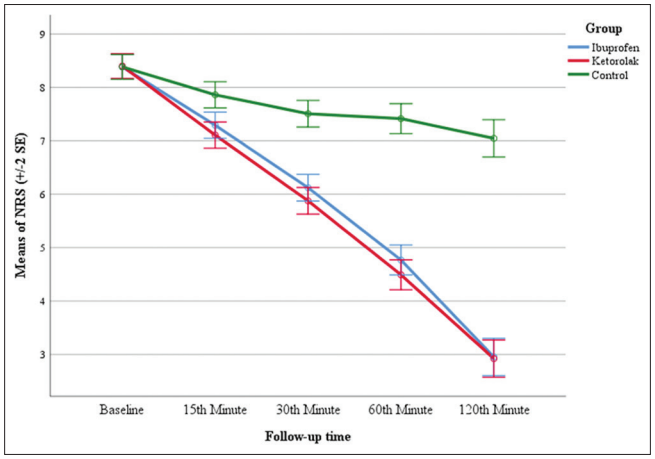

Figure 2: The pain severity among treatment groups based on the time of evaluation

adverse effects distribution had no significant difference in treatment groups (P = 0.629) [Table 2].

Discussion

This study compared the efficacy of IV morphine plus ibuprofen or ketorolac versus morphine alone in relieving renal colic pain. The severity of pain significantly decreased in all treatment groups in follow-up time interval and the reduction of pain in K group was significantly higher and in control group was significantly lower. The mean rescue analgesic dose was significantly higher in the control group and lower in K group. The efficacy of ketorolac plus morphine and ibuprofen plus morphine in the reduction of pain was similar but more than IV morphine alone.

Many studies investigated the efficacy of opioids and NSAIDs in controlling renal colic pain. Although there are limited number of studies comparing the combination of morphine with NSAIDs versus morphine alone, two studies investigated the efficacy of ketorolac, morphine, and combination of both in reducing renal colic pain and the results showed that combination treatment was more effective than monotherapy in reducing pain.[15,20] These results were consistent with ours. However, our study also investigated the efficacy of combination treatment of ibuprofen plus morphine.

On the other hand, the systematic review conducted by Gu *et al*. revealed that in the most of the studies, NSAIDs were more effective in more than 50% renal colic pain relief than opioids, combination of both or placebo and the superiority of NSAIDs could be its direct effect on inhibition of cyclooxygenase enzyme, but the combination therapy had significant priority compared to monotherapy in patients with uncontrollable renal colic pain with NSAIDs alone also in comparison of all outcomes including pain variance at 30 min, rescue analgesic requirements and acute adverse effects.[11]

Holdgate and Pollock reviewed the studies on controlling renal colic pain and 20 studies concluded that the administration of NSAIDs or opioids could significantly decrease the severity of pain, but only six studies found that pain severity score was lower in NSAIDs injection than opioids injection and the required rescue analgesia was lower in patients receiving NSAIDs than those receiving opioids. In addition, they declared that the difference was not clinically significant.[21] Shams Vahdati *et al*. showed that IV administration of the combination of 0.1 mg/kg morphine and 75 mg diclofenac had no priority than 1 gr paracetamol, in renal colic pain management.[22] Using another NSAIDs, different dose of morphine and considering morphine alone as a control group explained the different results.

Forouzanfar *et al*. concluded that the mean pain severity score in the group of patients receiving IV ibuprofen alone was significantly lower than those receiving IV ketorolac alone at 15th min. The number of completely relieved cases in ibuprofen group was twice more than the ketorolac group at the 60th min.[10] Shaker and Borghei compared the efficacy of 800 mg IV ibuprofen alone and 30 mg IV ketorolac alone in 70 patients with renal

colic pain. The results showed that the pain severity decreased within 60 min of injection in both groups, but the trend of the change in pain score was not statistically significant.[23] In contrast, our study showed no difference between IV ibuprofen and ketorolac because of the impact of adding 5 mg morphine to both treatment arms.

Consistent with our study, Hosseininejad *et al*. showed that gender and age had no significant difference among treatment groups of ketorolac, morphine, or the combination of both.[20] Forouzanfar *et al*. showed no significant difference between the treatment groups of ibuprofen and ketorolac in the category of gender, age, history of urolithiasis, and size or location of stone.[10] There was significant difference between treatment groups in terms of stones located at pelvis site.

In our study, adverse effects were not significantly different between the treatment groups. In this regard, Hosseininejad *et al*. showed that adverse effects had no significant difference among treatment groups of ketorolac, morphine, or the combination of both.[20] However, Gu *et al*. showed that in the most studies, NSAIDs like ibuprofen or ketorolac were the better choice of acute renal colic management because of lower adverse effects compared to opioids alone or combination of both.[11] Different kinds of administration, different dose of morphine, and different kind of NSAIDs used in this systematic review illustrate the different findings.

Some studies compared the adverse effects in monotherapies with NSAIDs or opioids in the management of renal colic. Holdgate and Pollock reported higher adverse effects of opioids than NSAIDs.[21] However, Golzari *et al*. found that the adverse effects were more frequent in patients taking NSAIDs compared to opioids. In the group of NSAIDs, IV administration of ketorolac caused more adverse effects than ibuprofen.[7] Forouzanfar *et al*. did not find any difference of adverse effects between patients receiving ibuprofen alone or ketorolac alone.[10]

The difference was related to the different sample size, the route and dose of drugs' administrations, and scales used for measuring the severity of pain.

Limitations

The pain intensity assessment is always based on self-reports which may be different between patients and may increase the degree of bias. The study did not assess the hemodynamic changes because of using low dose of morphine. Unfortunately, the history of taking any analgesics 6 h prior to ED admission was not considered as an exclusion criterion in this study while it could be a confounding variable and this study was done based on the approved study protocol.[24] Therefore, we recommend further clinical trials with more variables using the different pain intensity scales, evaluate the hemodynamic changes, and analyze the data after adjusting the possible associated and confounding variables to make the statistics closer to the reality.

Conclusion

As some studies suggested low efficacy of ibuprofen in controlling acute renal colic, morphine was used in all treatment groups in our study to prevent patient's suffering from uncontrolled pain. The results showed that the pain severity scores significantly decreased in all treatment groups from the 15th min after injection and the efficacy of IV ketorolac plus morphine and IV ibuprofen plus morphine was similar to each other but better than IV morphine alone.

Author contributions statement

AS: conceptualization; data curation; formal analysis; methodology; project administration; resources; supervision; validation; writing – review & editing. MT: data curation; investigation; methodology; visualization; writing – original draft. SB: data curation; investigation; visualization; writing – original draft; writing – review & editing. EA: data curation; visualization; writing – original draft; writing – review & editing. AM: methodology; data curation; investigation; visualization; writing – original draft; writing – review & editing. MS: conceptualization; methodology; project administration; resources; supervision; validation. MB: project administration; resources; supervision; validation.

Ethical approval

The implementation protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (code: IR. TUMS. VCR. REC.1398.844) on 6 August 2017.

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None.

Conflicts of interest

None Declared.

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