International Journal of Obstetric Anesthesia (2019) 38, 25–31
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https://doi.org/10.1016/j.ijoa.2018.12.002

ORIGINAL ARTICLE

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Comparison of the potency of phenylephrine and norepinephrine bolus doses used to treat post-spinal hypotension during elective caesarean section

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ABSTRACT
Background: Phenylephrine, although considered the vasopressor of choice, can cause reflex bradycardia and a fall in cardiac output. Norepinephrine, due to its direct positive chronotropic and reflex negative chronotropic actions, is expected to overcome this problem. However, limited information about its effective dose for management of post-spinal hypotension, and its potency compared to phenylephrine, is available.
Methods: One hundred consecutive patients who developed post-spinal hypotension were treated with a predetermined dose of either phenylephrine or norepinephrine. Correction of hypotension after one minute was considered 'success'. The starting dose for the first patient and testing interval (the incremental or decremental dosing) were 100 μg and 10 μg in the phenylephrine group, and 6 μg and 0.5 μg in the norepinephrine group. Doses for subsequent patients were determined by the responses of previous patients according to the Narayana rule for up-down sequential allocation. ED95 and ED50 of phenylephrine and norepinephrine boluses and their potency ratio were calculated.
Results: Using Probit analysis, ED95 and ED50 values were 43.1 μg (95% CI 39.5 to 65.0 μg) and 33.2 μg (95% CI 5.1 to 37.0 μg) for phenylephrine, and 3.7 μg (95% CI 3.5 to 4.7 μg) and 3.2 μg (95% CI 1.8 to 3.4 μg) for norepinephrine. The relative potency ratio of norepinephrine and phenylephrine was 11.3 (95% CI 8.1 to 16.9).
Conclusion: Based on the results of this study, norepinephrine is about 11 times more potent than phenylephrine. When used as bolus doses for treatment of hypotension, 100 μg phenylephrine should be approximately equivalent to 9 μg norepinephrine.

Keywords: Phenylephrine; Norepinephrine; Hypotension; Spinal anaesthesia; Caesarean section; Potency

Introduction

In obstetric patients, vasopressors remain the mainstay of management of post-spinal hypotension. Over the last decade, phenylephrine, an α-1 adrenergic agonist, has emerged as the vasopressor of choice.[1] It is a potent, rapidly-acting vasopressor with a short duration of action and it preserves fetal acid-base status better than ephedrine.[2] However, its principal drawback is reflex bradycardia which may result in a fall in cardiac output.[3] Phenylephrine is used as either intravenous boluses or an infusion during caesarean section. The most commonly used bolus dose is 100 μg.

Norepinephrine is a potent vasopressor with strong α-adrenergic receptor agonist and relatively weak β-adrenergic agonist actions, and its direct positive chronotropic action would be expected to limit bradycardia.[4] It has been used as a vasopressor in obstetric patients,[4–9] but little information about the preferred dose for management of post-spinal hypotension, or the potency ratio compared to phenylephrine, is available.[6,8]

The present study was conducted to calculate the 95% and 50% effective doses (ED95 and ED50) of norepinephrine and phenylephrine and their relative potency ratio when administered as a bolus for the treatment of hypotension in patients undergoing elective caesarean section under spinal anaesthesia.

Methods

This was a randomised double-blind dose-finding study which was conducted after approval from the Institutional Ethics Committee and obtaining written informed

Accepted December 2018
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consent from all patients prior to inclusion in the study. Patients were recruited from May 2017 to February 2018. The trial was prospectively registered at www.ctri.nic.in on 7th December 2016 (CTRI/2016/12/007542).

One hundred consecutive patients who developed hypotension after subarachnoid block were studied. Healthy females with a term, uncomplicated, singleton pregnancy undergoing elective caesarean section under spinal anaesthesia were included in the study. Those having maternal complications including diabetes, pre-eclampsia, cardiovascular disease, cerebrovascular disease, renal disease, absolute or relative contra-indications for spinal anaesthesia, baseline systolic blood pressure (SBP) less than 100 mmHg, mesenteric or peripheral vascular thrombosis or those taking monoamine oxidase inhibitors or tricyclic antidepressants were excluded from the study.

The patients were randomly divided into two groups of 50 each, using a computer-generated random number table according to the vasopressor to be used for treatment of hypotension. Sealed opaque envelopes numbered from 1 to 100 containing the drug names were made for allocation concealment. The vasopressor dose for each patient was decided according to the response of the previous patient using up-down sequential dose allocation. The dose calculations were performed by the first author (MM) who conveyed the dose to be used to the person preparing the test drug, neither of whom were involved in conduct of the case or observation of the drug response. The person observing the drug response and the patient were blind to the drug and dose allocation.

The patient was fasted for at least eight hours and given ranitidine 50 mg and metoclopramide 10 mg intravenously before transfer to the operation room. When the patient was supine on the operating table with a wedge under the right buttock, three readings of heart rate (HR) and SBP were averaged to give the baseline value for maternal HR and SBP. An 18-gauge intravenous cannula was inserted in the arm and a fluid co-load of 15 mL/kg Ringer's Lactate given, after which the rate of fluid infusion was reduced to 4 mL/kg/h. Subarachnoid block was performed in the sitting position at the L2-L3 or L3-L4 vertebral interspace, using a 25-gauge spinal needle in a midline approach. Either 2.2 mL (if 150 cm or more in height) or 2.0 mL (if shorter than 150 cm) hyperbaric bupivacaine 0.5% w/v was injected. The patient was then immediately turned supine and the wedge was placed under the right buttock.

Monitoring included continuous electrocardiography, HR, non-invasive blood pressure and pulse oximetry. Heart rate and SBP were noted before spinal anaesthesia and then every minute after spinal injection until the end of the study period. Post-spinal hypotension was defined as a fall of SBP $\geq$20% from the baseline or an absolute value of less than 100 mmHg, whichever was greater. If hypotension developed, a dose of either norepinephrine or phenylephrine was administered in a volume of 5 mL according to the patient's group and dose allocation.

If hypotension was corrected after one minute, the treatment was considered a success and the dose was termed effective. If SBP failed to return to above the threshold for treating hypotension, the treatment was considered ineffective and a phenylephrine 100 μg bolus was given. Any subsequent episodes of hypotension were also treated with rescue boluses of phenylephrine 100 μg.

The initial starting dose for the first patient in the phenylephrine group was 100 μg. Incremental or decremental doses of vasopressor used as part of the up-down sequential allocation were made in 10 μg steps. In the norepinephrine group the starting dose and the testing interval were 6 μg and 0.5 μg.

The doses for subsequent patients were determined by responses to all previous patients according to a variation of the Narayana rule for up-down sequential allocation. In this method, doses are clustered around the ED95.[10,11] If a patient had received a particular dose of a drug, the proportion of adequate responses in all the patients receiving that dose up to that point were calculated. If this proportion was >0.95, the next dose was decreased by 10 μg. If it was <0.95, the next dose was increased by 10 μg. The dose remained the same if this proportion was 0.95.

The study endpoint was response to the predetermined vasopressor bolus. The incidence of complications was recorded prior to the administration of rescue phenylephrine bolus or delivery of the fetus, whichever was earlier. Complications observed during this period, such as nausea, vomiting, dizziness etc. were recorded. If hypotension did not develop before delivery of the baby, the patient was excluded from further analysis and the next patient received the same drug and dose.

The primary outcome measures were calculation of ED95 of phenylephrine and norepinephrine boluses and their potency ratio. The secondary outcome measure was calculation of ED50 of phenylephrine and norepinephrine boluses.

Previous literature has described computer simulation in a range of scenarios to calculate a sample size for calculations of effective dose.[10,11] As the sample size commonly used for such calculations has been 40–50 patients per group,[8,11] it was decided to study 50 patients in each group.

SPSS-20 (IBM Corp, Armonk, NY) statistical software was used for statistical analysis. Continuous variables were summarised as mean $\pm$ standard deviation (SD) and/or median (interquartile range [IQR]),

depending on the skewness of data. Categorical variables were expressed as absolute numbers, frequency and proportions (%). For comparative analysis, Student's unpaired t-test was used to compare demographic and other patient characteristics, baseline haemodynamic variables, haemodynamic variables before and after vasopressor administration, and baby birth weight. Non-parametric data (time to events, volume of bupivacaine used and level of block) were compared using the Mann Whitney U test. Chi-square or Fisher's exact test was used to compare recurrence of hypotensive episodes and maternal complications. The ED95, ED50 and relative potency of the two vasopressors were calculated using Probit analysis.

Results

The CONSORT flow diagram for the study is shown in Fig. 1. The two groups were comparable with respect to demographic profile, other patient characteristics, various time intervals and baseline haemodynamic parameters (Table 1).

After Probit analysis, the ED95 and ED50 values for phenylephrine were 43.1 μg (95% CI 39.5 to 65.0 μg) and 33.2 μg (95% CI 5.1 to 37.0 μg) respectively, and for norepinephrine were 3.7 μg (95% CI 3.5 to 4.7 μg) and 3.2 μg (95% CI 1.8 to 3.4 μg) respectively. The relative potency ratio of norepinephrine and phenylephrine was 11.3:1 (95% CI 8.1 to 16.9). The sequence of effective and ineffective responses at each vasopressor dose level for successive patients is shown in Fig. 2 (phenylephrine) and Fig. 3 (norepinephrine). Response rates for each phenylephrine and norepinephrine dose used are summarised in Tables 2 and 3 respectively.

Table 4 shows the time to develop the first episode of hypotension after spinal injection, and SBP and HR just before and one minute after administration of vasopressor. There were no statistically significant differences in these variables. Four (8%) patients in group phenylephrine and five (10%) in group norepinephrine had a HR <60 beats/min, one minute after vasopressor administration.

Twenty-one (42%) patients in the phenylephrine group and 19 (38%) patients in the norepinephrine group developed further episodes of hypotension between administration of the test drug and delivery of the baby (P=0.838), and required phenylephrine rescue boluses for treatment.

Neonatal Apgar scores at 1- and 5-min were comparable (P=1.000). No neonate had an Apgar score of 7 or less. Neonatal birth weights were 2.7 ± 0.4 kg and 2.6 ± 0.4 kg in the phenylephrine and norepinephrine groups respectively (P=0.214).

Five patients (10%) developed nausea in the phenylephrine group and three of them (6%) had an episode of vomiting. In the norepinephrine group, three (6%) patients complained of nausea, and one (2%) vomited. No patient in either group developed dizziness or

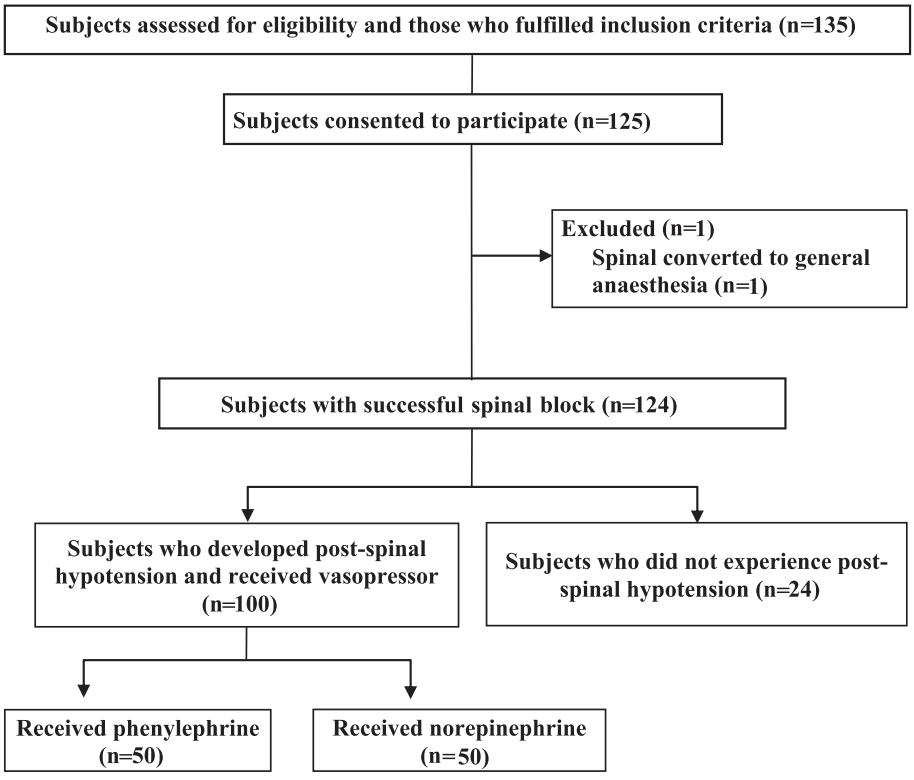

Fig. 1 CONSORT diagram

Table 1 Demographic and other patient variables

Maternal characteristic	Phenylephrine group (n=50)	Norepinephrine group (n=50)	*P*-value
Age (y)	25.7 ± 3.7	25.9 ± 3.6	0.83
Weight (kg)	62.2 ± 10.1	61.6 ± 10.2	0.53
Height (cm)	153.7 ± 5.6	153.0 ± 5.9	0.75
Period of gestation (weeks)	38.3 ± 1.2	38.6 ± 1.4	0.28
Volume of bupivacaine used (mL)	2.2 (2.0–2.2)	2.2 (2.0–2.2)	0.39
Level of block achieved	T6 (T6-T4)	T6 (T6-T4)	0.78
Fluid administered up to delivery (mL)	639 ± 260	694 ± 338	0.36
Spinal to skin incision (min)	3 (3–4)	3 (3–4)	0.80
Spinal to uterine incision (min)	10 (9.0–14.3)	10 (8.8–16.0)	0.65
Spinal to delivery (min)	12 (10–15.3)	12 (10–17.3)	0.53
Uterine incision to delivery (min)	1 (1–1)	1 (1–2)	0.15
Baseline systolic blood pressure (mmHg)	128.1 ± 10.8	127.4 ± 12.8	0.79
Baseline heart rate (beats/min)	92.4 ± 14.8	91.3 ± 15.3	0.74
Hypotensive value (mmHg)	105.2 ± 5.3	105.1 ± 6.8	0.94

Values are mean ± SD or median (IQR).

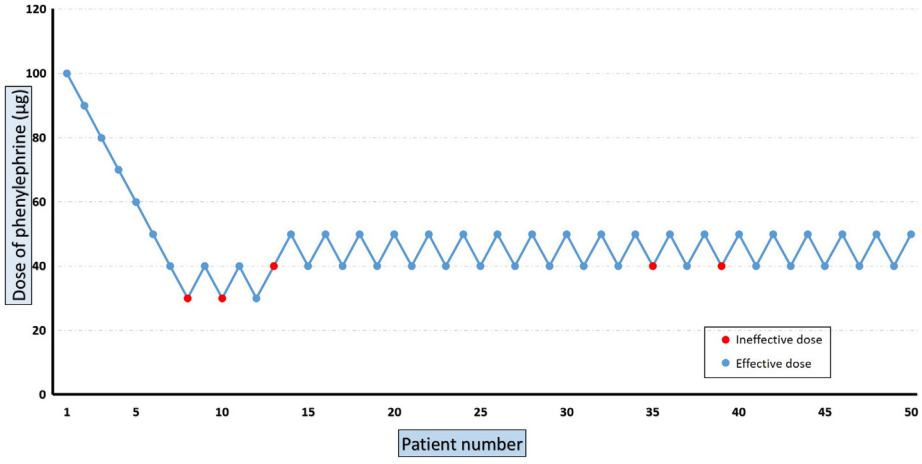

Fig. 2 Patients' response to assigned dose of phenylephrine

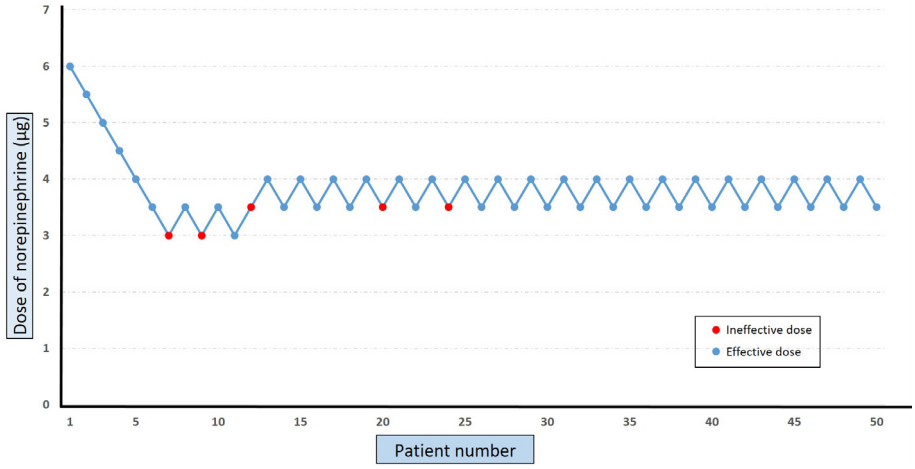

Fig. 3 Patients' response to assigned dose of norepinephrine

Table 2 Response rates for phenylephrine doses

Assigned dose (μg)	No. of patients	No. of successes	Successful response rate (%)
100	1	1	100
90	1	1	100
80	1	1	100
70	1	1	100
60	1	1	100
50	20	20	100
40	22	19	86
30	3	1	33

Table 3 Response rates for norepinephrine doses

Assigned dose (μg)	No. of patients	No. of successes	Successful response rate (%)
6	1	1	100
5.5	1	1	100
5	1	1	100
4.5	1	1	100
4	20	20	100
3.5	23	20	87
3	3	1	33

Table 4 Haemodynamic variables before and after administration of vasopressor

Haemodynamic variables	Phenylephrine group (n=50)	Norepinephrine group (n=50)	*P*-value
Time to develop first episode of hypotension (min)	5.0 (3.8–6.3)	5.0 (3.0–7.0)	0.95
Systolic blood pressure at first episode of hypotension (mmHg)	98.5 ± 10.4	99.8 ± 7.7	0.48
Systolic blood pressure 1-min after vasopressor administration (mmHg)	114.8 ± 11.9	114.3 ± 13.3	0.83
Heart rate at first episode of hypotension (beats/min)	99.1 ± 20.5	98.2 ± 20.6	0.82
Heart rate 1-min after vasopressor administration (beats/min)	79.7 ± 16.5	85.3 ± 19.6	0.13

Values are mean ± SD or median (IQR).

another maternal complication. There was no statistically significant difference in the incidence of complications between the groups (P=0.510 for nausea and 0.612 for vomiting).

Discussion

This study calculated the ED95, ED50 and potency ratio of phenylephrine and norepinephrine. The relative potency ratio was calculated as 11.3:1 (95% CI 8.1 to 16.9), so 100 μg phenylephrine should be approximately equivalent to 9 μg norepinephrine when used as a bolus dose for treatment of hypotension.

Initial comparative studies of phenylephrine and norepinephrine used a dose ratio of 20:1 for these vasopressors.[12–15] A similar ratio was used by Ngan Kee et al. when comparing computer-controlled infusions of phenylephrine or norepinephrine for maintenance of blood pressure during spinal anaesthesia for caesarean delivery.[4] They used infusions of norepinephrine 5 μg/mL and phenylephrine 100 μg/mL, and the required rate of vasopressor administration was greater in the norepinephrine group than in the phenylephrine group. It was suggested that the true potency ratio for norepinephrine and phenylephrine for maintaining blood pressure was probably less than 20:1 and the infusion rate requirements indicated a potency ratio of 16:1.

When planning our study, data on the potency of norepinephrine in relation to phenylephrine were very limited. The study was conducted to calculate the potency ratio of norepinephrine and phenylephrine by evaluating their ED95 and ED50, when administered as bolus doses for treatment hypotension in patients undergoing elective caesarean section under spinal anaesthesia. Based on Ngan Kee et al.'s findings,[4] 6 μg of norepinephrine was considered equivalent to 100 μg of phenylephrine, and so the starting doses for phenylephrine and norepinephrine in the present study were 100 μg and 6 μg respectively. The response to the vasopressor was assessed one minute after injection because the peak effects of phenylephrine and norepinephrine occur at 30–50 s and 22–45 s, respectively, after administration.[12]

Recently, evidence has emerged about doses of norepinephrine for management of post-spinal hypotension in obstetric patients. In 2017 Ngan Kee conducted a random-allocation, graded dose-response study in 180 healthy parturients undergoing elective caesarean section under spinal anaesthesia.[6] The relative potency ratio of the two vasopressors was estimated as 13.1 (95% CI 10.4 to 15.8) and the dose of norepinephrine equivalent to phenylephrine 100 μg was estimated as 7.6 μg. Hypotension was defined as greater than a 20% fall in SBP from baseline values. A single bolus of either norepinephrine 4, 5, 6, 8, 10, or 12 μg or phenylephrine 60, 80, 100, 120, 160, or 200 μg was administered to treat hypotension. The SBP after one minute was recorded as the percentage of the full correction of SBP to the baseline value. The ED50 values estimated in this study were 10 μg (95% CI 6 to 17 μg) for norepinephrine and 137 μg (95% CI 79 to 236 μg) for phenylephrine.

The ED50 values in our study, 3.2 μg (95% CI 1.8 to 3.4 μg) for norepinephrine and 33.2 μg (95% CI: 5.1 to 37.0 μg) for phenylephrine, were much lower than the values reported by Ngan Kee. The most likely reason is that Ngan Kee targeted full correction of SBP to the baseline value, whereas our end-point was the correction of SBP to the level at which treatment had become indicated. Differences in the patient populations could also have affected the results.

Onwochei et al. carried out another prospective, double-blind, sequential allocation dose-finding study to determine the ED90 of norepinephrine, when administered as intermittent intravenous boluses, for prevention of post-spinal hypotension in patients undergoing elective caesarean section.[8] Intermittent norepinephrine boluses of either 3, 4, 5, 6, 7, or 8 μg were administered whenever SBP was below 100% of baseline. Development of hypotension, defined as SBP <80% of the baseline value, was considered a failure. The first patient received a dose of 3 μg and the doses administered to the successive patients were determined by the response of the previous patient. The ED90 of norepinephrine for prevention of post-spinal hypotension was calculated as 5.49 μg (95% CI 5.15 to 5.83) using the truncated Dixon and Mood method, and 5.80 μg (95% CI 5.01 to 6.59) using the isotonic regression method. In that study, no comparison was made with phenylephrine. The ED90 calculated was much higher than ED95 values for norepinephrine in our study. This could be attributable to entirely different study designs, and the fact that Onwochei et al. administered norepinephrine for prevention of hypotension, whereas we used it for treatment of post-spinal hypotension.

In the present study, bradycardia was defined as a HR <60 beats/min. Although norepinephrine, when compared to phenylephrine, is expected to cause a lower incidence of bradycardia due to its β-agonist action in addition to α-agonism, the incidence of bradycardia one minute after vasopressor administration did not significantly differ between groups. The mean HR one minute after vasopressor administration did not differ. Ngan Kee et al. reported a greater fall in HR after phenylephrine administration.[4]

The safety profile of norepinephrine for the neonate is a potential concern. Apgar scores were assessed at one and five minutes and there were no significant differences between the phenylephrine and norepinephrine groups. It would be inappropriate to draw any conclusions about neonatal outcome from our study as hypotension recurred in several patients and the initial vasopressor dose failed in some. All such patients were administered phenylephrine 100 μg as a rescue vasopressor before delivery.

Our study has certain limitations. First, we studied the response to a single dose of vasopressor used to treat a first episode of hypotension. Many patients developed further episodes of hypotension after correction of the initial episode. The drug requirement for management of these was not studied. Second, our results are applicable only to the use of phenylephrine and norepinephrine for treatment of post-spinal hypotension and cannot be extrapolated to use of these vasopressors for prevention of hypotension. Lastly, neonatal outcome was assessed in the form of Apgar scores. This may not solely represent the effect of a particular vasopressor, since a phenylephrine bolus was used as a rescue vasopressor in both groups.

Based on the results of this study, we conclude that the ED95 and ED50 of single boluses of phenylephrine to treat post-spinal hypotension in elective caesarean delivery were 43.1 μg and 33.2 μg, respectively. The values for norepinephrine were 3.7 μg and 3.2 μg respectively. The relative potency ratio of norepinephrine and phenylephrine was 11.3:1 (95% CI 8.1 to 16.9). Phenylephrine 100 μg should be approximately equivalent to norepinephrine 9 μg when used as a bolus dose for treatment of hypotension.

Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

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