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Editorial

Noradrenaline for haemodynamic control in obstetric anaesthesia: Is it now a suitable alternative to phenylephrine?

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Single-shot spinal anaesthesia (SA) is the neuraxial technique used most often for routine elective caesarean section (CS), as it is easier, quicker and less costly than combined spinal-epidural anaesthesia (CSE). It is also more reliable than epidural anaesthesia (EA) for providing effective sensory block. However, compared with CSE or EA, SA has the disadvantage of inducing a rapid onset dense sympathetic block that almost inevitably results in hypotension that may be severe if not adequately prevented; this in turn may lead to adverse maternal and neonatal consequences [1,2]. The search for the optimal management of hypotension in this setting has therefore become one of the most active areas of research in obstetric anaesthesia.

In this issue, *Anaesthesia Critical Care & Pain Medicine* is publishing a randomised controlled study comparing noradrenaline (norepinephrine) (NA) *versus* phenylephrine (PE) infusion for prophylaxis of spinal hypotension during elective CS [3]. There are now many studies published on NA use in this context, with related recent meta-analyses and systematic reviews [4]. However, this is the first randomised controlled double-blind trial (RCDBT) that compares NA *versus* PE, as it will be most often administrated in *clinical* practice, i.e. as a *manually titrated* infusion (in an adequate 1:15 approximately equipotent ratio); while also using a standard intrathecal dose (hyperbaric bupivacaine 10 mg + fentanyl 10 μg) and a recommended rapid co-load infusion of lactated Ringer's solution (15 mL/kg) [5]. The main findings were similar effectiveness of NA *versus* PE to maintain maternal blood pressure, with lower number of physician interventions and possibly lower incidence of reactive hypertension and bradycardia. It is therefore a useful addition to the growing evidence that NA is a suitable, and possibly superior, alternative to PE (discussed below).

However, it should be acknowledged that some aspects of the study design are unclear or suboptimal, which may make it difficult to draw clear conclusions from the results; therefore, they should be viewed as exploratory rather than firm evidence. First, based on the declared primary outcome and power analysis, this study was designed to determine superiority between groups for the incidence of hypotension. Today, this may no longer be the optimal primary outcome to choose because, given that PE and NE are both potent vasoconstrictors, it is not clear why one would expect a 30% difference in efficacy between them. Further, any difference that did occur would be most likely attributable to differences in relative dosage regimen rather than any inherent difference in vasopressor effectiveness. The primary outcome was indeed not different between groups. From a methodological point of view, this finding also needs to be interpreted carefully, as a non-significant test for superiority does not show equivalence, but merely that no difference was detected. Second, given the (unsurprising) lack of difference for the primary outcome, the discussion and conclusions focus on the secondary outcomes, including number of physician interventions, bradycardia and reactive hypertension incidences. The authors state that "post-hoc pairwise comparison was performed using Bonferroni test", but there were in fact a large number of other secondary outcomes included, and it is unclear if Bonferroni corrections was applied to account for the total number of these secondary outcomes. In other words, there is concern for inflated risk of type 1 error. Third, the treatment of hypotension in both groups included a bolus of PE or even ephedrine (if heart rate < 75 bpm), whereas it would have been more logical to keep on using NA as rescue boluses in the NA group to have a "cleaner" comparison between the two vasopressors studied and a better potential to detect differences between them.

Where are we nowadays?

The RCDBT by Ngan Kee et al. [6] proposed NA use in 2015 as a potential alternative to PE, which is the vasopressor widely accepted today as the recommended first-line agent. Since then, all the subsequent trials have confirmed that NA and PE are similarly effective for maintaining maternal blood pressure provided that they are used in an equipotent ratio (ranging from 1:13 to 1:16). The current study by Hasanin et al. [3] is in agreement with these other recent studies and further strengthens them by confirming

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the findings in a *clinical* practice setting based on a *manually titrated* NA infusion.

The remaining issues are whether there are potential advantages of using NA over PE and if so, whether they are clinically relevant and not counterbalanced by potential risks or disadvantages for the mother and/or the neonate. First, maternal bradycardia is much less likely to occur using NA than PE. This has been consistently shown in most studies adequately powered for this outcome (the current study by Hasanin et al. [3] also showed a trend towards less bradycardia with NA but this was not statistically significant because of insufficient power), although additional studies are still needed to quantify more clearly the magnitude of this effect. Of clinical relevance, NA may not only lessen the incidence of bradycardia but may also reduce its severity, compared with PE. This is quite obvious when actually using the drug. Of note, there are rare cases of maternal collapse reported during onset of SA for CS that are preceded by maternal bradycardia related to a sudden decrease in venous return rather than the bradycardic effect of PE itself. Nonetheless, given the severity of this rare complication, using a vasopressor such as NA that does not add baroreflex bradycardia seems intuitively advantageous. Second, maternal cardiac output has been shown to be on average 10% higher with NA *versus* PE during prophylactic infusion [4,6]. Whether this is a clinical benefit remains unclear given that it has been shown that cardiac output increases initially after induction of SA and tends to simply return to baseline value during PE prophylactic infusion [7]. However, when a high rate of PE infusion is used ($\approx$ 100 mcg/min), cardiac output may decrease by up to $\approx -20\%$ from baseline value [8]; as pointed out by Hasanin et al. [3], further studies are thus specifically needed in high-risk pregnancies to determine whether NA may prevent this decrease and produce potential beneficial effects for the mother and/or the neonate. Third, NA may possibly better protect the mother from reactive hypertension compared with PE because of quicker offset when the infusion is reduced or stopped [3,9]. The above may explain why Hasanin et al. [3] found less physician interventions were required with NA *versus* PE. Fourth, it might be expected that NA would produce less nausea and/or vomiting than PE, as a result of the higher maternal cardiac output with similar blood pressure. This is however not the case in almost all studies published [4]. This suggests that this much disturbing maternal side effect is mainly related to pressure-dependent effects rather than flow-dependent effects.

The potential risks and disadvantages of NA over PE remain a subject of debate. The concern for maternal tissue ischaemia during NA extravasation from peripheral veins when using a diluted solution (e.g., 5–10 mcg/ml) is no different than when an equipotent concentration of PE is used. This was nicely addressed in the editorial by Vallejo et al. [10].

Importantly, care must be taken when assessing publications to identify which NA preparation has been used (i.e., brand name and manufacturer) and most importantly if the NA concentration is expressed as NA *base* or NA *bitartrate*, since base is twice as potent as bitartrate formulation (i.e., 5 mcg/ml of NA base = 10 mcg/ml of NA bitartrate) [11]. The vast majority of countries worldwide uses NA *base*, which is the pharmacologically active part of the vasopressor, to express the NA concentration as required by their national agency. However, this is not the case in France where NA *bitartrate* formulation is used to express the NA concentration as per French agency request (ANSM) [11]. This may also occur in some other countries (e.g., in Africa and Asia) that import NA from the manufacturer (Aguettant) in France. In the current study of Hasanin et al. [3], one assumes that the NA concentration of 4 mcg/mL is expressed as NA *base*, but this remains unclear as it was not explicitly stated.

The last issue is whether NA provides better [6], identical [12] or worse neonatal outcome [13] compared with PE, as assessed with surrogate markers such as umbilical arterial pH (UA pH), lactate, oxygen content, and catecholamines. This cannot be fully detailed here. Cooper [13] raised concerns about cases of foetal acidosis that occurred in a dose-finding study of intermittent boluses of NA [14] with no obvious explanation provided, although it is unclear whether ephedrine was used as a rescue vasopressor. Most other RCDBTs comparing NA and PE did not find or did not report differences in neonatal outcomes, except the initial study by Ngan Kee et al. [6] that found that neonates in the NA group *versus* the PE group had slight but statistically significant better UA pH, UA oxygen content and lower UA catecholamines (adrenaline and noradrenaline). A recent large randomised, double-blind, pragmatic non-inferiority trial, presented in part at the Obstetric Anaesthetists' Association (OAA) meeting in May 2019, of 533 elective and 135 non-elective patients found no difference in UA pH (NA *vs.* PE: 7.289 ± 0.049 *vs.* 7.287 ± 0.046) nor in UA base excess (-4.8 ± 2.8 *vs.* -4.9 ± 2.8 mmol/L) [12]. Although reassuring, more research is still needed to fully understand these unclear discrepancies among studies.

In conclusion, as NA use is relatively new for haemodynamic control during caesarean section performed under SA, accumulation of more evidence is still necessary. The study of Hasanin et al. [3] is therefore an interesting opportunity to expand our knowledge on this hot topic. In line with previous studies, it suggests that NA is as effective as PE when infused for maintenance of maternal blood pressure with no greater side effects. Nonetheless, more information is still needed about the comparative effects of NA and PE, particularly regarding maternal nausea and neonatal outcomes. The advantages of NA over PE likely include less maternal bradycardia and greater cardiac output. NA might also allow a more precise and easier titration around the targeted blood pressure, because of quicker offset of action that could result in less reactive hypertension. Thus, provided that one pays attention to prevent drug dilution errors, NA can now be considered a reasonable alternative to PE for routine use. The current dynamic international research on this topic will tell us in the near future if NA can be further recommended to actually replace PE as first-line vasopressor in obstetrics: a nice perspective...

Disclosure of interest

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References

[1] Mercier FJ, Augè M, Hoffmann C, Fischer C, Le Gouez A. Maternal hypotension during spinal anesthesia for caesarean delivery. Minerva Anestesiol 2013;79:62–73.
[2] Ngan Kee WD. The use of vasopressors during spinal anaesthesia for caesarean section. Curr Opin Anaesthesiol 2017;30:319–25. http://dx.doi.org/10.1097/ACO.0000000000000453.
[3] Hasanin A, Amin S, Refaat S, Habib S, Zayed M, Abdelwahab Y, et al. Norepinephrine versus phenylephrine infusion for prophylaxis against post-spinal anaesthesia hypotension during elective caesarean delivery: A randomised controlled trial. Anaesth Crit Care Pain Med 2019. http://dx.doi.org/10.1016/j.accpm.2019.03.005 (in press).
[4] Wang X, Shen X, Liu S, Yang J, Xu S. The Efficacy and Safety of Norepinephrine and Its Feasibility as a Replacement for Phenylephrine to Manage Maternal Hypotension during Elective Cesarean Delivery under Spinal Anesthesia. Biomed Res Int 2018;2018:1869189. http://dx.doi.org/10.1155/2018/1869189.
[5] Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, et al. International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia 2018;73:71–92. http://dx.doi.org/10.1111/anae.14080.
[6] Ngan Kee WD, Lee SWY, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood

pressure during spinal anesthesia for cesarean delivery. Anesthesiology 2015;122:736–45. http://dx.doi.org/10.1097/ALN.0000000000000601.

[7] Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, et al. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology 2009;111:753–65. http://dx.doi.org/10.1097/ALN.0b013e3181b437e0.

[8] Stewart A, Fernando R, McDonald S, Hignett R, Jones T, Columb M. The dose-dependent effects of phenylephrine for elective cesarean delivery under spinal anesthesia. Anesth Analg 2010;111:1230–7. http://dx.doi.org/10.1213/ANE.0b013e3181f2eae1.

[9] Ngan Kee WD, Khaw KS, Tam Y-H, Ng FF, Lee SW. Performance of a closed-loop feedback computer-controlled infusion system for maintaining blood pressure during spinal anaesthesia for caesarean section: a randomized controlled comparison of norepinephrine versus phenylephrine. J Clin Monit Comput 2017;31:617–23. http://dx.doi.org/10.1007/s10877-016-9883-z.

[10] Vallejo MC, Zakowski MI. Old ways do not open new doors: norepinephrine for first-line treatment of spinal hypotension. Anesth Analg 2018;126:1809–11. http://dx.doi.org/10.1213/ANE.0000000000002491.

[11] Noradrénaline: Résumé des Caractéristiques du Produit. Available at http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0302303.htm.(accessed October 18, 2019).

[12] Ngan Kee WD, Ng FF, Lee SWY, Lee A. Norepinephrine versus phenylephrine during spinal anaesthesia for caesarean delivery: a randomized double-blinded pragmatic non-inferiority study comparing neonatal outcome. IJOA 2019;39. http://dx.doi.org/10.1016/j.ijoa.2019.02.006 [S7O.1].

[13] Cooper DW. Bolus Norepinephrine Administration and Fetal Acidosis at Cesarean Delivery Under Spinal Anesthesia. Anesth Analg 2018;126:1087. http://dx.doi.org/10.1213/ANE.0000000000002755.

[14] Onwochei DN, Ngan Kee WD, Fung L, Downey K, Ye XY, Carvalho JCA. Norepinephrine intermittent intravenous boluses to prevent hypotension during spinal anesthesia for cesarean delivery: a sequential allocation dose-finding study. Anesth Analg 2017;125:212–8. http://dx.doi.org/10.1213/ANE.0000000000001846.

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