Optimisation hémodynamique per-Césarienne (sous Rachianesthésie)

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ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Conflits d'intérêt potentiels :

- **Laboratoire AGUETTANT® :**

  → produit l'éphédrine, la phényléphrine et la noradrénaline

« Optimisation HD » *per-César sous RA (programmée)*
→ « *Qui fait quoi ?* »

- <u>Choisissez une des 3 propositions</u> :

  A- Je ne fais ***pas de*** **prophylaxie** (= je ne traite qu'en cas d'hypotension)

  B- Je fais une **prophylaxie avec de l'*éphédrine***

  (ou un mélange éphédrine-phényléphrine)

  C- Je fais une **prophylaxie avec de la *phényléphrine***

  D- Je fais une **prophylaxie avec de la *noradrénaline***

Hypotension *: définition*

- Définition : nombreuses … mais …
  - ↘ **de la PA systolique** (PAS) de **plus de 20%** par rapport à la valeur de base
  - En d'autres termes : une *PAS < 80% de la valeur de base*

Anaesthesia 2018, 73, 71–92 doi:10.1111/anae.14080

Guidelines

International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia

S. M. Kinsella,[1] B. Carvalho,[2] R. A. Dyer,[3] R. Fernando,[4] N. McDonnell,[5] F. J. Mercier,[6] A. Palanisamy,[7] A. T. H. Sia,[8] M. Van de Velde[9,10] and A. Vercueil[11]

Kinsella SM et al., Anaesthesia 2018; 73: 71-92

Rachianesthésie "single-shot" pour Césarienne programmée :

→ 50% à 80-90% d'hypotension

(en l'absence de prévention)

Mercier FJ et al., Minerva Anaestesiol 2013; 79: 62-73
Ngan Kee WD et al., Curr Opin Anaesthesiol 2017; 30: 319-25
Kinsella SM et al., Anaesthesia 2018; 73: 71-92

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Table 1 Comparison of commonly used vasopressors.

	Ephedrine	Phenylephrine	Metaraminol	Noradrenaline	Adrenaline	Mephentermine
Receptor	β1, β2, weak α	α1	α1, weak β	α1, β	α1, β	α1, β
Mechanism	Indirect, weak direct	Direct	Direct and indirect	Direct	Direct	Indirect
Onset	Slow	Immediate	1–2 min	Immediate	Immediate	Immediate
Duration	Prolonged	Intermediate	Prolonged	Short	Short	Prolonged

Hypotension *: conséquences*

Maternelles

- Nausées & Vomissements, Dyspnée !…
- Perte de Conscience ± Inhalation
- Collapsus CV, IDM,…

Fœtales/Néonatales

- Acidose (pHa bas)
- RCF anormal, Apgar bas
- Réa Néonatale, IMC, décès

Mercier FJ et al., Minerva Anaestesiol 2013; 79: 62-73
Ngan Kee WD et al., Curr Opin Anaesthesiol 2017; 30: 319-25
Kinsella SM et al., Anaesthesia 2018; 73: 71-92

Hypotension *: mécanisme(s)*

PA ≈ RVS x DC

- ↘ *très rapide (dès les 1ères min) et très forte de la post-charge*,

  car **début très rapide d'une forte vasodilatation artérielle** après l'injection intrathécale

- *Pas de* ↘ notable *de la pré-charge* (i.e., pas de ↘ du retour veineux), au moins initialement,

  car la ***vasodilatation veineuse*** est plus *modérée* et son début se fait plus *lentement*

- Ainsi le *débit cardiaque (DC) est maintenu et même augmenté* initialement, lors de la rachiA

  ➢ **La ↘ de PA n'est due qu'à la ↘ des résistances vasculaires systémiques** (RVS), au départ (i.e., pas à la ↘ du DC)

Van Dyk D et al., Best Pract Res Clin Anaesthesiol. 2022; 36: 69-82
Kinsella SM et al., Anaesthesia 2018; 73: 71-92
Kuhn JC et al., Anesth Analg 2016; 122: 1120-1129

Hypotension *: Moyens pour la prévenir et/ou la traiter*

- Méthodes non-pharmacologiques
  - Réduction de la stase veineuse dans les M. Inf. (BAT)
  - « Tilt » gauche ≈ 10-15° (prévention compression cave)

- **Méthodes pharmacologiques**

PA ≈ RVS x DC

  - Remplissage vasculaire i.v. ; soit :

    1- *pré*-remplissage par cristalloïdes : inefficace

    2- *pré*-remplissage par colloïdes (HEA) : banni ...

    3- *co*-remplissage par cristalloïdes : partiellement efficace (si débit rapide post-rachi)

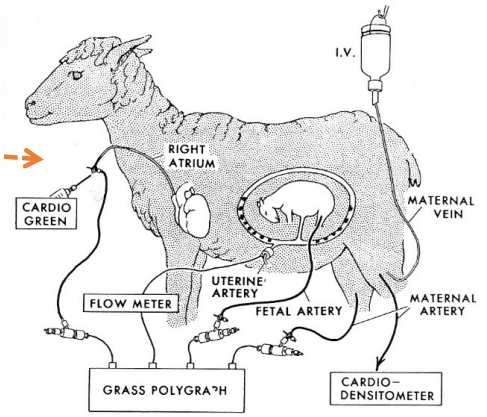
  - **Vasopresseurs** : phényléphrine ± éphédrine, noradrénaline…

Sharwood-Smith G, Br J Anaesth 2005; 96: 100-5
Mercier FJ et al., Minerva Anaestesiol 2013; 79: 62-73
Ngan Kee WD et al., Curr Opin Anaesthesiol 2017; 30: 319-25
Kinsella SM et al., Anaesthesia 2018; 73: 71-92

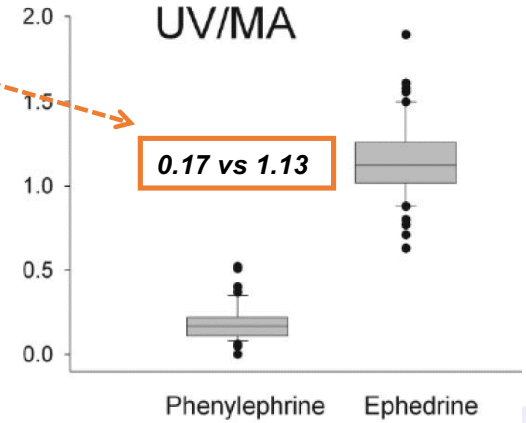
Ephédrine : le *gold standard* du 20ème siècle, mais pas du 21ème …

- Années 70 à 90' : études expérimentales sur la brebis gravide…
- Mais la placentation chez l'homme est très spécifique :
  → l'éphédrine passe librement la "barrière" placentaire chez la femme enceinte : 1.13 = **113%** !
- Ainsi, l'éphédrine augmente la VO_2 fœtale (par action β+ agoniste), tandis que l'hypotension ↘ l'apport fœtal en O_2 : « double peine »

→ **acidose fœtale dose-dépendante, parfois sévère** (pHa < 7,00)



(Ralston, Anesthesiology 1974)



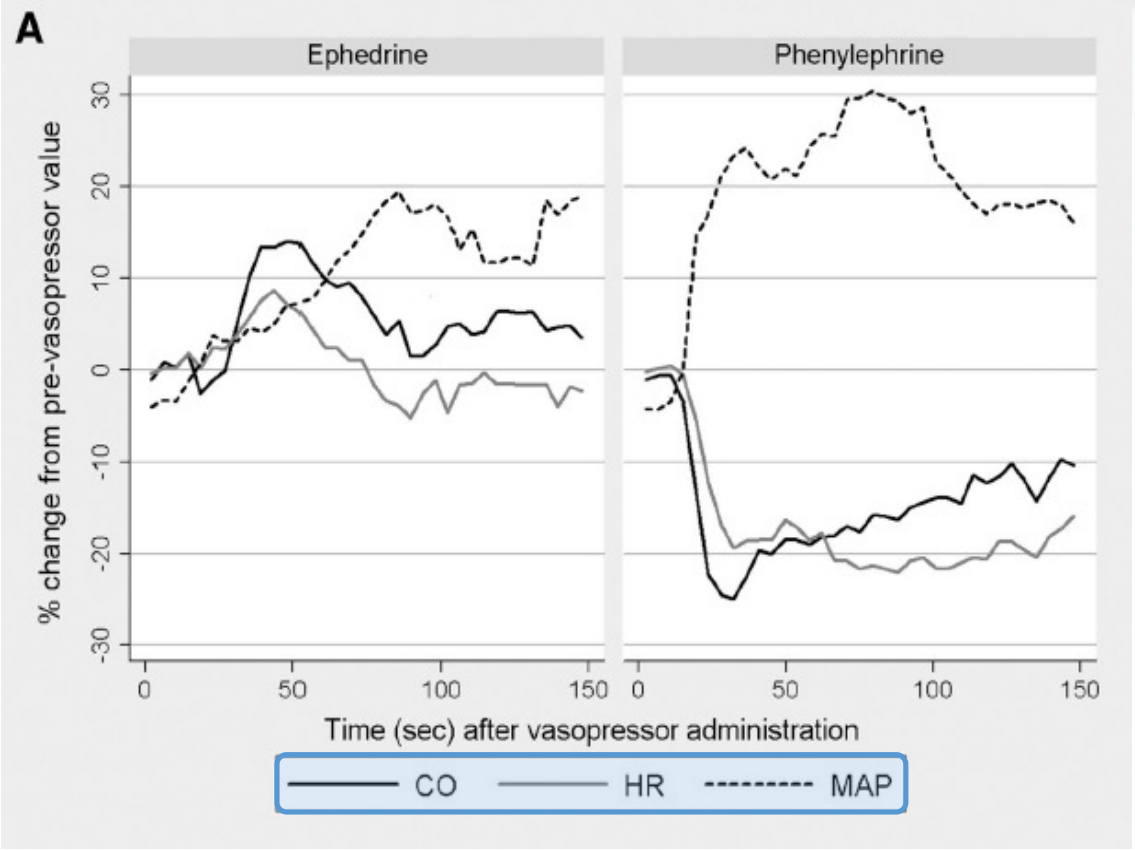
(Ngan Kee, Anesthesiology 2009)

Phényléphrine : est devenu vasopresseur de 1ère ligne (depuis 2005-2010)

- Faible transfert placentaire dans l'espèce humaine : **17%** seulement
- **α-agoniste pure :**
  - vasoconstricteur pur, bien adapté pour antagoniser la vasodilatation induite par la rachiA
  - Pas d' ↗ de la VO_2 fœtale (car pas d'action béta-agoniste)
- Pas de vasoconstriction délétère significative sur la circulation utéro-placentaire dans l'*espèce humaine*
- Habituellement, **pas d'acidose fœtale, quelle que soit** la dose nécessaire :
  - Si la PHE est utilisée (au lieu de l'Ephédrine) & et si l'hypotension est brève (< 2-3 min)

Hemodynamic effects of Ephedrine, Phenylephrine … during SA for elective CD

Dyer RA et al., Anesthesiology 2009; 111: 753-65



NB : dose totale d'éphédrine ≤ 10-**15 mg**, pour éviter l'acidose fœtale

Phényléphrine : *Quand ?*

- Phényléphrine **prophylactique >> réactive/curative** :

↘↘ N-V (mais pHa à peine meilleur)

Ngan Kee, Br J Anaesth 2004

↘ hypotension & N-V : RR = **0,36** [0,18-0,73] & **0,39** [0,17-0,91]

Heesen, Anaesthesia 2014

Phenylephrine : *Comment ?*

- en pratique, **maintenir la PA entre 90 - 100%** de la valeur de base :

  - **Avec la Phényléphrine *prophylactique en* perfusion**,

    → commencée à 25-50 µg/min, puis adaptée/ajustée

    Kinsella SM et al., Anaesthesia 2018; 73: 71-92

  - *ou* avec des bolus *prophylactiques de* 50 µg de phényléphrine,

    → dès que la PAS ↘ (avec prise de la PA toutes les 1 min)

Anaesthesia 2018, 73, 71–92 doi:10.1111/anae.14080

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Kinsella SM et al., Anaesthesia 2018; 73: 71-92

International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia

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Recommandations 2018 : points-clefs

Anaesthesia 2018, 73, 71–92 doi:10.1111/anae.14080

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- Vasopresseur **prophylactique** → d'emblée après la rachi
- **α-agonistes** plus "physiologiques" ; **phényléphrine** recommandée → ***Janvier 2018*** :

> α-agonist drugs are the most appropriate agents to treat or prevent hypotension following spinal anaesthesia. Although those with a small amount of β-agonist activity may have the best profile (noradrenaline (norepinephrine), metaraminol), phenylephrine is currently recommended due to the amount of supporting data. Single-dilution

4 études sur la NA,
dont 3 études du groupe de W. Ngan Kee

versus

35 études sur la PE

Kinsella SM et al., Anaesthesia 2018; 73: 71-92

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→ ***Début 2022*** :

4 ans de littérature en plus depuis ces guidelines

→ ***Plus de 30 études sur la NA / César***

Kinsella SM et al., Anaesthesia 2018; 73: 71-92

"Landmark RCT" avec la noradrénaline lors de la César/rachi : 2015

- PSE iv automatisé par ordinateur en boucle rétrocontrôlée :
  → pour maintenir la PAS à 100% de la valeur de base :
    - avec la Noradrénaline (NA) à 5 µg/ml
    - ou la Phényléphrine (PE) à 100 µg/ml → **1:20** ratio for NA:PE
- Résultats :
  - PAS → idem (pas surprenant) – mais pas de différence aussi pour les VES
  - **Meilleur Débit Cardiaque** & **moins de bradycardie** (BC) avec la NA :
    - **DC** (/ base) : maintenu à **103% vs. 94%** (avec NA vs. PE)
    - **BC** : **18% vs. 56%**

Ngan Kee WD et al., Anesthesiology 2015; 122(4): 736-45

“Landmark RCT” avec la noradrénaline lors de la César/rachi : 2015

Table 2. Neonatal Outcome

	Norepinephrine Group	Phenylephrine Group	*P* Value
Birth weight (kg)	3.11 [2.85–3.37]	3.19 [3.04–3.36]	0.37
Apgar score at 1 min <8	0	0	
Apgar score at 5 min <8	0	0	
Umbilical arterial blood gases			
pH	7.30 [7.28–7.33]	7.29 [7.28–7.32]	0.45
Pco_2 (mmHg)	50 [48–56]	52 [48–56]	0.77
Po_2 (mmHg)	15 [13–18]	14 [11–16]	0.20
Base excess (mmol/l)	−2.0 [−3.7 to −1.0]	−2.4 [−4.2 to −0.8]	0.87
Oxygen content (ml/dl)	6.0 [4.4–7.7]	5.2 [3.8–7.0]	0.29
Umbilical venous blood gases			
pH	7.35 [7.34–7.37]	7.34 [7.32–7.36]	0.031
Pco_2 (mmHg)	41 [38–43]	41 [38–45]	0.69
Po_2 (mmHg)	27 [23–30]	26 [23–28]	0.23
Base excess (mmol/l)	−3.2 [−4.1 to −2.0]	−3.5 [−5.6 to −2.4]	0.06
Oxygen content (ml/dl	12.7 [11.3–14.4]	11.8 [9.6–13.7]	0.047

Values are median [interquartile range] or number.

Ngan Kee WD et al., Anesthesiology 2015; 122(4): 736-45

NA : contrôle de la PA plus précis qu'avec la PE ?

J Clin Monit Comput
DOI 10.1007/s10877-016-9883-z

ORIGINAL RESEARCH

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

Warwick D. Ngan Kee[1] · Kim S. Khaw[1] · Yuk-Ho Tam[1] · Floria F. Ng[1] · Shara W. Lee[2]

Received: 5 January 2016 / Accepted: 25 April 2016

Abstract Closed-loop feedback computer-controlled vasopressor infusion has been previously described for maintaining blood pressure during spinal anaesthesia for caesarean section but there are limited data available comparing the relative performance of different vasopressors. The aim of this study was to compare the performance of norepinephrine versus phenylephrine in this system. Data from a randomized, two-arm parallel group, double-blinded controlled trial were reanalyzed. 104 patients scheduled for elective caesarean section under spinal anaesthesia were randomized to receive computer-controlled closed-loop infusion of either norepinephrine 5 μg ml^{-1} or phenylephrine 100 μg ml^{-1}. This was started immediately after wobble was smaller (2.85 [2.07–5.17] %) versus 3.39 [2.62–4.90] %, $P = 0.028$) in the norepinephrine group versus the phenylephrine group. Divergence was similar between groups. The precision of the control of blood pressure was greater with norepinephrine compared with phenylephrine at the drug concentrations used.

Keywords Caesarean section · Hypotension · Vasopressors · Computer-control

1 Introduction

Ngan Kee WD et al., 2017

Prevention of hypotension after spinal anaesthesia for caesarean section: a systematic review and network meta-analysis of randomised controlled trials

J. P. Fitzgerald,[1] **K. A. Fedoruk,**[2,3] **S. M. Jadin,**[1] **B. Carvalho**[4] and **S. H. Halpern**[2,5]

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4 Professor, Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA

Summary

Spinal anaesthesia for caesarean section commonly causes maternal hypotension. This systematic review and network meta-analysis compared methods to prevent hypotension in women receiving spinal anaesthesia for caesarean section. We selected randomised controlled trials that compared an intervention to prevent hypotension with another intervention or inactive control by searching MEDLINE and Embase, Web of Science to December 2018. There was no language restriction. Two reviewers extracted data on trial characteristics, methods and outcomes. We assessed risk of bias for individual trials (Cochrane tool) and quality of evidence (GRADE checklist). We assessed 109 trials (8561 women) and 12 different methods that resulted in 30 direct comparisons. Methods ranked by OR (95%CI) from most effective to least effective were: metaraminol 0.11 (0.04–0.26); norepinephrine 0.13 (0.06–0.28); phenylephrine 0.18 (0.11–0.29); leg compression 0.25 (0.14–0.43); ephedrine 0.28 (0.18–0.43); colloid given before induction of anaesthesia 0.38 (0.24–0.61); angiotensin 2, 0.12 (0.02–0.75); colloid given after induction of anaesthesia 0.52 (0.30–0.90); mephentermine 0.09 (0.01–1.30); crystalloid given after induction of anaesthesia 0.78 (0.46–1.31); and crystalloid given before induction of anaesthesia 1.16 (0.76–1.79). Phenylephrine caused maternal bradycardia compared with control, OR (95%CI) 0.23 (0.07–0.79). Ephedrine lowered umbilical artery pH more than phenylephrine, standardised mean difference (95%CI) 0.78 (0.47–1.49). We conclude that vasopressors should be given to healthy women to prevent hypotension during caesarean section with spinal anaesthesia.

hypotension après RA pour César
Network meta-analysis of RCTs

109 études (8561 patients),
12 différentes méthodes préventives
30 comparaisons directes

Critère principal = hypotension

NA ≥ PE

(bradyC avec PE & pH plus bas avec Eph)

Fitzgerald et al., Anaesthesia 2019

A systematic review of phenylephrine vs. noradrenaline for the management of hypotension associated with neuraxial anaesthesia in women undergoing caesarean section

M. Heesen,[1] **N. Hilber,**[2] **K. Rijs,**[3] **R. Rossaint,**[4] **T. Girard,**[5] **F.J. Mercier**[6] and **M. Klimek**[7]

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6 Professor, Department of Anaesthesia, A. Béclère Hospital – APHP & Paris-Saclay University, Clamart, France

Summary

Phenylephrine is recommended for the management of hypotension after spinal anaesthesia in women undergoing caesarean section. Noradrenaline, an adrenergic agonist with weak β-adrenergic activity, has been reported to have a more favourable haemodynamic profile than phenylephrine. However, there are concerns that noradrenaline may be associated with a higher risk of fetal acidosis, defined as an umbilical artery pH < 7.20. We performed a systematic review of trials comparing noradrenaline with phenylephrine, concentrating on primary outcomes of fetal acidosis and maternal hypotension. We identified 13 randomised controlled trials including 2002 patients. Heterogeneity among the studies was high, and there were too few data to calculate a pooled effect estimate. Fetal acidosis was assessed in four studies that had a low risk of bias and a low risk of confounding, that is, studies which used a prophylactic vasopressor and where women received the allocated vasopressor only. There were no significant differences between these studies. No significant differences were observed for hypotension. Two trials found a significantly lower incidence of bradycardia when using noradrenaline. Cardiac output was significantly higher after noradrenaline in two of three studies. For other secondary outcomes including nausea, vomiting and Apgar scores at 1 and 5 min, no studies found significant differences. The evidence so far is too limited to support an advantage of noradrenaline over phenylephrine. Concerns of a deleterious effect of noradrenaline on fetal blood gas status cannot currently be assuaged by the available data from randomised controlled studies.

hypotension après RA pour César
Revue systématique - PE *vs*. NA

13 « RCTs » (2020 patients) :

Acidose fœtale (4) : pas de différence
Hypotension (13) : pas de différence
Bradycardie (2) : moins avec la NA
DC (2 sur 3) : plus élevé avec la NA

Heesen et al., Anaesthesia 2020

March, A&A 2018

REFERENCES

1. Anwari JS. An environment is more than a climate. *Anesth Analg*. 2018;126:1086.
2. Katz JD. Control of the environment in the operating room. *Anesth Analg*. 2017;125:1214–1218.
3. Katz JD, Holtzman RS, Vinson A. Occupational health. In: Barash PG, Cullen BF, Stoelting RK, et al. *Clinical Anesthesia*. 8th ed. Philadelphia, PA: Wolters Kluwer; 2017:65–90.

DOI: 10.1213/ANE.0000000000002744

Bolus Norepinephrine Administration and Fetal Acidosis at Cesarean Delivery Under Spinal Anesthesia

To the Editor

I was very interested to read this article by Onwochei et al.[1] It presented the results from a dose-finding study of intermittent intravenous boluses of norepinephrine given to prevent hypotension during spinal anesthesia for cesarean delivery. A previous study by Ngan Kee et al[2] has shown that an infusion of norepinephrine given to maintain arterial pressure compared favorably with the current gold standard, phenylephrine.

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REFERENCES

1. 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;125:212–218.
2. Ngan Kee WD, Lee SW, 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;122:736–745.
3. Cooper DW, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2002;97:1582–1590.

DOI: 10.1213/ANE.0000000000002755

In Response

We would like to thank Dr Cooper for his interest in our article and appreciate his points about fetal acidosis.[1]

Our study was designed to determine the effective bolus

Anaesthesia 2021, 76, 743–747 doi:10.1111/anae.15363

Editorial

Noradrenaline – at best it is not worse. A comparison with phenylephrine in women undergoing spinal anaesthesia for caesarean section

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2 Professor, Department of Anaesthesia, University Hospital Basel, Basel, Switzerland
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Vasopressor drugs for the prevention and treatment of hypotension during neuraxial anaesthesia for Caesarean delivery: a Bayesian network meta-analysis of fetal and maternal outcomes

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Part of this paper was presented at the 51st annual meeting of the Society for Obstetric Anesthesia and Perinatology, Phoenix, AZ, USA (May 2019).

Abstract

Background: The optimal choice of vasopressor drugs for managing hypotension during neuraxial anaesthesia for Caesarean delivery is unclear. Although phenylephrine was recently recommended as a consensus choice, direct comparison of phenylephrine with vasopressors used in other healthcare settings is largely lacking. Therefore, we assessed this indirectly by collating data from relevant studies in this comprehensive network meta-analysis. Here, we provide the possible rank orders for these vasopressor agents in relation to clinically important fetal and maternal outcomes.

Methods: RCTs were independently searched in MEDLINE, Web of Science, Embase, The Cochrane Central Register of Controlled Trials, and clinicaltrials.gov (updated January 31, 2019). The primary outcome assessed was umbilical arterial base excess. Secondary fetal outcomes were umbilical arterial pH and P_{CO_2}. Maternal outcomes were incidences of nausea, vomiting, and bradycardia.

Results: We included 52 RCTs with a total of 4126 patients. Our Bayesian network meta-analysis showed the likelihood that norepinephrine, metaraminol, and mephentermine had the lowest probability of adversely affecting the fetal acid-base status as assessed by their effect on umbilical arterial base excess (probability rank order: norepinephrine > mephentermine > metaraminol > phenylephrine > ephedrine). This rank order largely held true for umbilical arterial pH and P_{CO_2}. With the exception of maternal bradycardia, ephedrine had the highest probability of being the worst agent for all assessed outcomes. Because of the inherent imprecision when collating direct/indirect comparisons, the rank orders suggested are possibilities rather than absolute ranks.

Conclusion: Our analysis suggests the possibility that norepinephrine and metaraminol are less likely than phenylephrine to be associated with adverse fetal acid-base status during Caesarean delivery. Our results, therefore, lay the scientific foundation for focused trials to enable direct comparisons between these agents and phenylephrine.

Vasopresseurs et RA pour César
a Bayesian
network meta-analysis of RCTs

52 RCTs (4126 patients)

Critère principal = BE art. ombilical

NE > PE > Eph

Singh et al.,
Br J Anaesth 2020

In summary, compared with other clinically used vasopressors in the obstetric setting, ephedrine appears to be the most likely agent to adversely affect fetal and maternal outcomes (except maternal bradycardia). Phenylephrine, currently recommended as a consensus choice and better ranked than ephedrine in our analysis, may not be the best vasopressor. Our analysis suggests the possibility that norepinephrine and metaraminol are less likely to adversely affect fetal acid-base status. More research into these agents and preferably multi-drug trials are required to improve the strength of the evidence and inform clinical practice.

Norepinephrine or phenylephrine during spinal anaesthesia for Caesarean delivery: a randomised double-blind pragmatic non-inferiority study of neonatal outcome

Warwick D. Ngan Kee[1,2,*], Shara W. Y. Lee[3], Floria F. Ng[1] and Anna Lee[1]

British Journal of Anaesthesia, 125 (4): 588–595 (2020)

Abstract

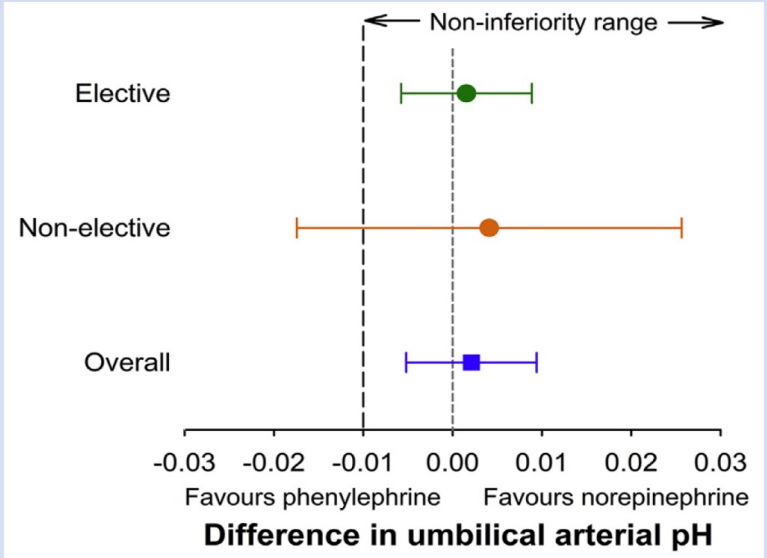
Background: Norepinephrine is an effective vasopressor during spinal anaesthesia for Caesarean delivery. However, before it can be fully recommended, possible adverse effects on neonatal outcome should be excluded. We aimed to test the hypothesis that umbilical arterial cord pH is at least as good (non-inferior) when norepinephrine is used compared with phenylephrine for treatment of hypotension.

Methods: We enrolled 668 subjects having elective and non-elective Caesarean delivery under spinal or combined spinal–epidural anaesthesia in this randomised, double-blind, two-arm parallel, non-inferiority clinical trial. Arterial blood pressure was maintained using norepinephrine 6 μg ml^{-1} or phenylephrine 100 μg ml^{-1} according to the practice of the anaesthetist, either prophylactically or therapeutically, as an infusion or bolus. The primary outcome was umbilical arterial pH with a chosen non-inferiority margin of 0.01 units.

Results: Of 664 subjects (531 elective and 133 non-elective) who completed the study, umbilical arterial cord blood was analysed for 351 samples from 332 subjects in the norepinephrine group and 343 samples from 332 subjects in the phenylephrine group. Umbilical arterial pH was non-inferior in the norepinephrine group (mean, 7.289; 95% confidence interval [CI], 7.284–7.294) compared with the phenylephrine group (mean, 7.287; 95% CI, 7.281–7.292) (mean difference between groups, 0.002; 95% CI, −0.005 to 0.009; $P=0.017$). Subgroup analysis confirmed the non-inferiority of norepinephrine for elective cases but was inconclusive for non-elective cases.

Conclusions: Norepinephrine was non-inferior to phenylephrine for neonatal outcome assessed by umbilical arterial pH. These results provide high-quality evidence supporting the fetal safety of norepinephrine in obstetric anaesthesia.

In summary, we identified no detrimental effect of norepinephrine on neonatal outcome compared with phenylephrine when used for maintaining BP during spinal and CSE anaesthesia for Caesarean delivery. Our results support a growing body of evidence that suggests that norepinephrine is a suitable agent for use in obstetric anaesthesia.



	Norepinephrine group	Phenylephrine group	P Value
Birth weight (kg)	3.00 (0.52)[a]	3.02 (0.53)[b]	0.67
Apgar score at 1 min <7	10/369 (27%)	10/352 (28%)	0.73
Apgar score at 5 min <7	4/369 (1%)	0/352 (0%)	0.12[†]
Umbilical arterial blood gases			
pH[‡]	7.289 (0.049)[c]	7.286 (0.048)[d]	0.57
P_{CO_2} (kPa)	6.3 (1.0)[c]	6.3 (1.1)[d]	0.95
P_{O_2} (kPa)	2.2 (0.5)[e]	2.2 (0.7)[f]	0.60
Base excess (mmol L^{-1})	−4.8 (2.7)[c]	−5.0 (2.8)[d]	0.48
Umbilical venous blood gases			
pH	7.338 (0.047)[g]	7.335 (0.044)[h]	0.22
P_{CO_2} (kPa)	5.4 (0.9)[g]	5.4 (0.9)[h]	0.72
P_{O_2} (kPa)	3.3 (0.8)[i]	3.3 (0.8)[j]	0.63
Base excess (mmol L^{-1})	−4.3 (2.7)[g]	−4.5 (2.5)[h]	0.40

"Landmark RCT" avec la noradrénaline lors de la César/rachi : 2015

Umbilical arterial and UV plasma concentrations of norepinephrine and UA plasma concentration of norepinephrine were lower in the norepinephrine group than in the phenylephrine group. Because catecholamines are not thought to readily cross the placenta,[29] these findings probably reflect differences in fetal catecholamine production. Fetal catecholamine levels have been shown to be greater with increased stress during delivery and fetal asphyxia,[29,30] and an inverse correlation has been shown between umbilical blood catecholamine concentrations and Po_2.[31] In our study, lower umbilical plasma catecholamine concentrations together with greater UV pH and oxygen content in the norepinephrine group suggest the possibility of decreased fetal stress in this group compared with the phenylephrine group which could be related to greater uteroplacental oxygen delivery. However, it should be noted that differences observed in our study were small, and the clinical significance of these findings in our low-risk patients is unclear.

Table 3. Umbilical Cord Plasma Concentrations of Epinephrine, Norepinephrine, Glucose, and Lactate

	Phenylephrine Group	Norepinephrine Group	*P* Value
Umbilical arterial			
Epinephrine (pg/ml)	400 [227–700]	281 [78–491]	0.042
Norepinephrine (pg/ml)	2,178 [1,403–3,921]	1,756 [1,048–2,435]	0.035
Glucose (mg/dl)	46 [43–52]	53 [48–60]	<0.001
Lactate (mmol/l)	1.8 [1.6–2.0]	2.0 [1.7–2.4]	0.088
Umbilical venous			
Epinephrine (pg/ml)	40 [18–73]	23 [18–63]	0.16
Norepinephrine (pg/ml)	457 [281–647]	347 [225–486]	0.031
Glucose (mg/dl)	51 [44–56]	56 [51–62]	<0.001
Lactate (mmol/l)	1.8 [1.6–2.0]	2.0 [1.6–2.4]	0.33

Values are median [interquartile range].

Ngan Kee WD et al., Anesthesiology 2015; 122(4): 736-45

ELSEVIER

SFAR
Société Française d'Anesthésie et de Réanimation

Editorial

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

Frédéric J. Mercier[a,*], Mickaël Soued[a], Estelle Morau[b], Warwick D. Ngan Kee[c]

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[b]*Département d'Anesthésie Réanimation, Centre Hospitalier Narbonne, 11100 Narbonne, France*
[c]*Department of Anaesthesiology, Sidra Medicine, Doha, Qatar*

→ ***La NA peut être considérée maintenant une alternative raisonnable à la PE***

- *Des études complémentaires restent bien sûr nécessaires*
- ***Pas de solution diluée** de NA encore disponible pour l'usage en Anesthésie*
- *10 µg de **NA tartrate** = 5 µg de **NA base***

Editorial/Anaesth Crit Care Pain Med 38 (2019) 591–593

Fluid loading for cesarean delivery under spinal anesthesia : toward a better understanding and optimal management

Mercier FJ, Anesth Analg 2011; 113: 677-80

CRYSTALLOID PRELOAD (VERSUS CONTROL OF NO FLUID)

Crystalloid preloading (10–20 mL/kg Ringer lactate solution) has been widely used for decades for the prevention of hypotension. However, the 1993 landmark study by Rout et al.[12] demonstrated that the incidence of hypotension was only slightly reduced in the group receiving 20 mL/kg crystalloid preload compared with a control group without a preload (55% vs 71%, respectively), whereas the severity of hypotension was unchanged and the ephedrine requirements were not reduced. Jackson et al.[13] reached the same conclusion regarding crystalloid preloading inefficacy (1000 vs 200 mL), despite the concomitant use of prophylactic ephedrine infusion in both groups. Moreover, Park et al.[14] found no benefit of crystalloid preload even when increasing volumes from 10 up to 30 mL/kg. In addition, umbilical arterial pH was not improved. Thus, the minimal effectiveness, if any, of crystalloid preload was clearly confirmed during the 1990s, and this technique is no longer recommended.[6,8]

British Journal of Anaesthesia **113** (3): 459–67 (2014)
Advance Access publication 26 June 2014 · doi:10.1093/bja/aeu103

BJA

OBSTETRICS

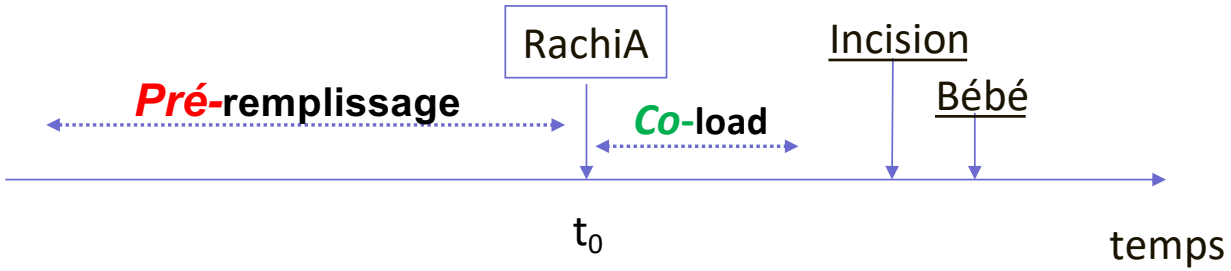
6% Hydroxyethyl starch (130/0.4) *vs* Ringer's lactate preloading before spinal anaesthesia for Caesarean delivery: the randomized, double-blind, multicentre CAESAR trial‡

F. J. Mercier[1]*, P. Diemunsch[2], A.-S. Ducloy-Bouthors[3], A. Mignon[4], M. Fischler[5], J.-M. Malinovsky[6], F. Bolandard[7], A. G. Aya[8], M. Raucoules-Aimé[9], D. Chassard[10], H. Keita[11], A. Rigouzzo[12] and A. Le Gouez[1], the CAESAR Working Group†

Table 2 Haemodynamic variables. All data provided in the table are from induction of spinal anaesthesia to delivery, cumulative during this time period and in ITT population unless otherwise indicated; *'Incidence of hypotension (ITT and PP)', the primary outcome, is provided with one-sided *P*-values (all other *P*-values are two-sided). ITT, intention-to-treat population, PP, per-protocol population; SAP, systolic arterial pressure; †symptomatic hypotension=SAP <80% of baseline + nausea and/or vomiting and/or dizziness; HR, heart rate; ‡bradycardia, HR <50 beats min^{-1}

	HES group		RL group		*P*-value
	n	*n* (%) or mean (SD) or median (range)	*n*	*n* (%) or mean (SD) or median (range)	
Incidence of hypotension, ITT*	82	30 (37%)	85	47 (55%)	0.025
Incidence of hypotension, PP*	68	23 (34%)	72	40 (56%)	0.019
Incidence of symptomatic hypotension†	82	3 (4%)	85	12 (14%)	0.028
SAP<70% baseline	82	8 (10%)	85	15 (18%)	0.14
SAP, minimum recorded ITT (mm Hg)	82	98 (14)	85	94 (14)	0.058
SAP, minimum recorded PP (mm Hg)	68	99 (14)	72	93 (14)	0.015
Duration of hypotension (min)	30	2.0 (0–20)	47	2.0 (1–10)	0.36
HR, minimum recorded (beats min^{-1})	82	62 (10)	85	61 (10)	0.19
Incidence of bradycardia‡	82	9 (11%)	85	11 (13%)	0.70
Atropine use	82	8 (10%)	85	8 (9%)	0.94
Phenylephrine requirements (μg), ITT	82	350 (50–1800)	85	350 (50–1250)	0.26
Phenylephrine requirements (μg), PP	68	350 (50–1800)	72	400 (50–1250)	0.075

Pré- vs. *Co-*remplissage



Prevention of hypotension during SA for CD : An effective technique using combination phenylephrine infusion and crystalloid cohydration

Ngan Kee WD et al, Anesthesiology 2005; 103: 744-50

Table 2. Hemodynamic Changes, Fluid, and Vasopressor Requirement

	Group 0	Group 1	*P* Value
Total intravenous fluid, ml	50 [40–60]	1,975 [1,609–2,010]	< 0.0001
Rate of intravenous fluid infusion, ml/min	1.7 [1.5–2.4]	63.5 [53.7–74.4]	< 0.0001
Total phenylephrine dose, μg	1,400 [1,145–1,818]	1,160 [753–1,568]	0.008
Rate of phenylephrine administration, μg/min	55.9 [46.3–63.6]	42.1 [30.4–52.3]	< 0.0001
Incidence of hypotension	15 (28.3%)	1 (1.9%)	0.0001
Minimum recorded SBP, mmHg	95 [89–106]	107 [98–110]	0.0002
Incidence of hypertension	25 (47%)	25 (47%)	1.0
Maximum recorded SBP, mmHg	139 [129–147]	140 [128–149]	0.83
Incidence of bradycardia (HR < 50 beats/min)	13 (24.5%)	9 (1.8%)	0.34
Minimum recorded HR, beats/min	53 [50–58]	58 [52–63]	0.013
Atropine required	0	0	1.0

Values are median [interquartile range] or number (%).

HR = heart rate; SBP = systolic blood pressure.

Left Lateral Table Tilt for Elective Cesarean Delivery under Spinal Anesthesia Has No Effect on Neonatal Acid–Base Status

A Randomized Controlled Trial

Allison J. Lee, M.D., Ruth Landau, M.D., James L. Mattingly, C.R.N.A., Margaret M. Meenan, C.R.N.A., Beatriz Corradini, M.Sc., Shuang Wang, Ph.D., Stephanie R. Goodman, M.D., Richard M. Smiley, M.D., Ph.D.

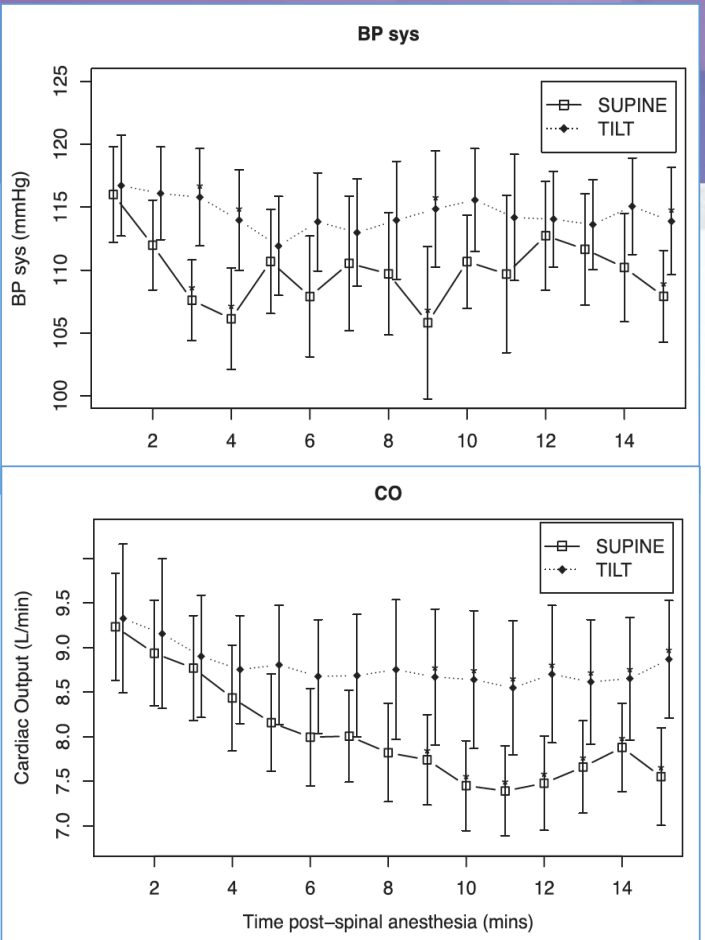
ABSTRACT

Background: Current recommendations for women undergoing cesarean delivery include 15° left tilt for uterine displacement to prevent aortocaval compression, although this degree of tilt is practically never achieved. We hypothesized that under contemporary clinical practice, including a crystalloid coload and phenylephrine infusion targeted at maintaining baseline systolic blood pressure, there would be no effect of maternal position on neonatal acid base status in women undergoing elective cesarean delivery with spinal anesthesia.

Methods: Healthy women undergoing elective cesarean delivery were randomized (nonblinded) to supine horizontal (supine, n = 50) or 15° left tilt of the surgical table (tilt, n = 50) after spinal anesthesia (hyperbaric bupivacaine 12 mg, fentanyl 15 μg, preservative-free morphine 150 μg). Lactated Ringer's 10 ml/kg and a phenylephrine infusion titrated to 100% baseline systolic blood pressure were initiated with intrathecal injection. The primary outcome was umbilical artery base excess.

Results: There were no differences in umbilical artery base excess or pH between groups. The mean umbilical artery base excess (± SD) was −0.5 mM (± 1.6) in the supine group (n = 50) *versus* −0.6 mM (± 1.5) in the tilt group (n = 47) ($P = 0.64$). During 15 min after spinal anesthesia, mean phenylephrine requirement was greater ($P = 0.002$), and mean cardiac output was lower ($P = 0.014$) in the supine group.

Conclusions: Maternal supine position during elective cesarean delivery with spinal anesthesia in healthy term women does not impair neonatal acid–base status compared to 15° left tilt, when maternal systolic blood pressure is maintained with a coload and phenylephrine infusion. These findings may not be generalized to emergency situations or nonreassuring fetal status. **(Anesthesiology 2017; XXX:0-0)**



Phenylephrine Use. The mean phenylephrine dose administered during the 15 min after spinal anesthesia and at delivery was significantly greater in the supine group: 789 ± 321 (n = 49) *versus* the tilt group −611 ± 228 (n = 48) ($P = 0.002$),

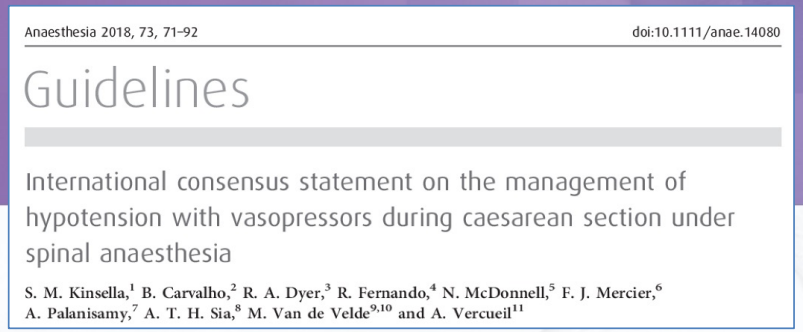
NARRATIVE REVIEW ARTICLE

Aortocaval Compression Syndrome: Time to Revisit Certain Dogmas

Allison J. Lee, MD, and Ruth Landau, MD

Anesth Analg 2017; 125: 1975-85

Recommandations 2018 : points-clefs



- Vasopresseur **prophylactique** → d'emblée après la rachi
- **α-agonistes** plus "physiologiques" ; **phényléphrine** recommandée → Janvier 2018
- Tilt G^{che} et co-remplissage par cristalloïdes ou pré-remplissage par colloïdes (et inciser sans retard)
- **But = PAS > 90% valeur de base**, pour éviter hypoTA < 80% valeur de base (PA mesurée / 1 min)
- Perfusion débit variable → débuter à 25-50 µg.min-1 (100 µg.ml^{-1} à 15-30 ml.h^{-1}) de phényléphrine, plus bolus QSP (ou bolus prophylactiques seuls)
- *FC maternelle = substitut pour le débit cardiaque*
- Faibles doses d'éphédrine pour les hypotensions avec FC basses (anticholinergiques seulement si bradycardie + hypotension significatives)
- *Pompes intelligentes informatisées (Smart pumps) : TA plus stables*
- Pré-éclampsie – commencer avec doses plus faibles (et sans PSE)
- *Cardiaques – décision adaptée à chaque cas*

Kinsella SM et al., Anaesthesia 2018; 73: 71-92

“baby” Noradrénaline : synthèse des avantages potentiels / PhénylE

- **Moins de Bradycardie** : en fréquence, mais aussi et surtout en intensité
- **Meilleur DC** : impact clinique moins évident
- **Durée plus courte** : améliore la précision du contrôle de la PA & réduit ainsi le risque de surdosage (“*reactive hypertension*”)
- **Au moins aussi bien sur le plan néonatal**, et peut être même un peu mieux !

- **NA tartrate à 10 µg/mL en France** **(= NA base 5 µg/mL)**

→ perf. ≈ **0,5 à 1 mL/min = 30 à 60 mL/h**

(soit 5 à 10 µg/min = 0,3-0,6 mg/h)

« Optimisation HD » *per-César sous RA (programmée)*
→ « *Qui fait quoi ?* »

- <u>Choisissez une des 3 propositions</u> :

  A- Je ne fais ***pas de*** **prophylaxie** (= je ne traite qu'en cas d'hypotension)

  B- Je fais une **prophylaxie avec de l'*éphédrine***

  (ou un mélange éphédrine-phényléphrine)

  C- Je fais une **prophylaxie avec de la *phényléphrine***

  D- Je fais une **prophylaxie avec de la *noradrénaline***

« Optimisation HD » *per-César sous RA (programmée)*
→ « *Qui fait quoi ?* »

- Choisissez une des 3 propositions :

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(ou un mélange éphédrine-phényléphrine)

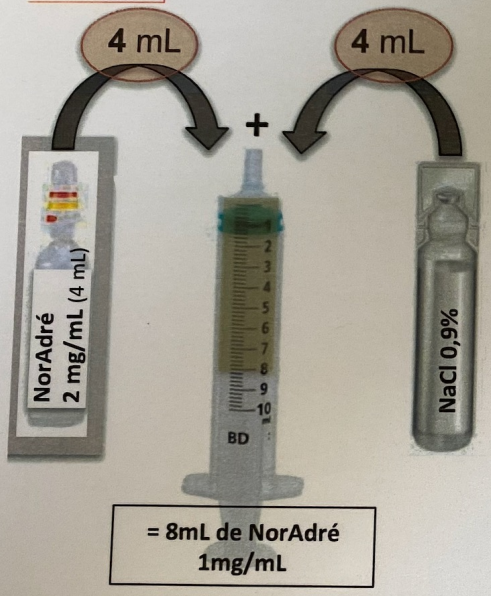
C- Je fais une **prophylaxie avec de la *phényléphrine***

D- Je fais une **prophylaxie avec de la *noradrénaline*** 🙂

NORADRÉNALINE POUR CÉSARIENNE PROGRAMMÉE

- protocole de pratique clinique à 10 µg/mL -

ÉTAPE 1



= 8mL de NorAdré 1mg/mL

ÉTAPE 2

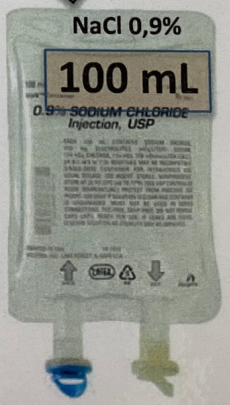
1 mL

= 1 mL de NorAdré 1 mg/mL

+ jeter la seringue de 10 mL de l'étape 1

ÉTAPE 3

1 mL

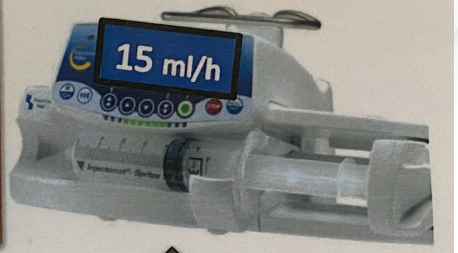


Objectif : **TA 90-100% de sa valeur de base**

Débuter **à 15 ml/h dès l'induction anesthésique via VVP** (Octopus® 3 voies)

Adapter la vitesse **selon TA prise toutes les 1 min** (palier de 15 mL/h).

→ débit moyen jusqu'à extraction fœtale : **30 mL/h**
→ débit maximal attendu : **60 mL/h**



ÉTAPE 4

= Noradrénaline 10 µg/mL

DAR ABC
Pr Mercier Dr Augé
Le 04/01/2019

BECAR
BÉCLÈRE
Anesthésie Réanimation

Séminaires BECAR 2022

Hôtel Novotel Paris Centre Bercy

Lun 28/11 et Mar 29/11 :

Anesthésie-Réanimation Obstétricale

Mer 30/11 et Jeu 01/12 :

Quoi de neuf en Anesthésiologie

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