Norepinephrine for Spinal Anesthesia-Induced Hypotension in Parturients

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Spinal Anesthesia-Induced Hypotension

Undesired repercussion[1,2]
- SNS predominates in pregnancy[3]
- SNS and PNS imbalance[4]

Exaggerated sympatholytic effects[4]
- Acute vasomotor blockade of sympathetic nerves[1,2]
- Activation of cardioinhibitory receptors[1,2]
- Pooling of up to 20% of blood volume[3]

Parturients undergoing cesarean section
- SAIH incidence 7.4% to 74.1%[4]

Maternal and Neonatal Adverse Effects

- Altered consciousness and decreased cardiac output[1,4]
- Splanchnic hypoperfusion leads to emetogenic serotonin release[1]
- Decreased cerebral perfusion and oxygenation stimulate vomiting[4,5]
- Decreased placental and fetal perfusion[4]
- Oxypurines and lipid peroxides found in umbilical blood[4]
- Acidosis and depressed Apgar scores[1]

2018 International Consensus Statement

Recommendations
- PE is the drug of choice for SAIH[1]
- More data is needed to recommend NE[1]
- Infusions are superior to bolus injections[1,6]

Norepinephrine vs. Phenylephrine

Norepinephrine	Phenylephrine
Potent α1-agonist[7]	**Potent** α1-agonist[10]
Mild β1-agonism[8]	**Lacks** β-agonism[11]
• Oppose baroreflexive bradycardia and decreased CO	• No direct chronotropic or inotropic effects
• Cardiac index increases with limited increase in HR or MVO_2[9]	• Effects on cardiac output are complex[12]
	• Dosing, volume status, HR, sympathetic tone

Research Question

- **P** In parturients receiving SA for cesarean section,
- **I** how do intravenous norepinephrine infusions
- **C** compared to intravenous phenylephrine infusions
- **O** affect SAIH and related adverse effects
- **T** during the intraoperative period?

Literature Review

- **Texas Medical Center Library Online Portal**
  - PubMed, EMBASE, Cochrane Library, CINAHL, Ovid MEDLINE
- **Filters**
  - 2013-2024, Humans, English language, randomized controlled trial, article
- **Aides**
  - Boolean operator 'AND,' snowballing technique
- **MeSH* & Key Terms**
  - Norepinephrine*, phenylephrine*, hypotension*, spinal anesthesia*, obstetrics*

15 randomized controlled trials

Levels and Grades of Evidence

Oxford Centre for Evidence-Based Medicine[13]		United States Preventive Services Task Force[14]	
Level 1	Systematic review	A	High certainty of net benefit 5
Level 2	RCTs 15	B	Benefit in eligible patients 10
Level 3	Non-RCTs	C	No recommendation for or against
Level 4	Case series	D	Routine use not recommended
Level 5	Mechanism based reasoning	I	Insufficient evidence

Population

Inclusion Criteria		Exclusion Criteria
ASA score < III[6,8,15-27]	Pre-eclampsia[22]	Pre-eclampsia[6-8,15-21,23-27]
≥18 years old[6,8,15-27]		Cardiovascular disease[6,8,15-27]
Term[6,8,15-17,19-21,23-27]	> 32 weeks[18,22]	
Singleton[6,8,15-18,20-27]	Twins[8,16,18,19]	Coagulation disorders[6,8,15-27]
SA for CS[6,8,15-27]	Non-elective[8,15]	

Study Design

Local Anesthetic
- 7.5-15 mg of 0.5% bupivacaine[6,8,15-18,20-27]
- 12 mg of 0.5% ropivacaine[19]

Drug Adjuncts
- 2.5-5 mcg sufentanil[16,19]
- 100-200 mcg PF morphine[16,27]
- 10-25 mcg fentanyl[8,15,21,23-27]
- No adjunct[6,17,18,22]

Crystalloid Co-load
- 10 - 20 mL/kg[17,20,23,26]
- 0.5 - 1 L[15,16,19,27]
- ≤ 2 L[6,8,21,24]
- No co-load[18,22,25]

NE-to-PE Potency
- 5:1 to 13:1[16,18,19,20,22,27]
- 15:1 to 20:1[6,8,15,17,21-26]
- (Dose at which two different drugs are equipotent)[28]

Norepinephrine vs. Phenylephrine Drips
- 0.05 mcg/kg/min NE vs. 0.1-0.75 mcg/kg/min PE[15,16,20,22,23,27]
- 2.5-6 mcg/min NE vs. 40-100 mcg/min PE[6,8,16,17,19,22,23]
- Started at the time of spinal or immediately after[6,8,15-24]

Approach to Treating Hypotension
- Titration of drips[8,16,21,23,24]
- 50-100 mcg PE or 5-15 mg ephedrine based on HR[16,23,27]
- 2.5-8 mcg NE vs. 25-100 mcg PE[6,8,15,17-22,24-26]

Outcomes

Maternal

Hypotension
- No difference[6,8,15,19-23,26]
- Higher in PE group*[16,17,25]
- Higher in NE group*[18]
- Rescue bolus requirements
  - No difference[6,8,15,16,18,21-23,27]
  - Higher in PE group*[17,25]

Bradycardia
- Higher in PE group*[6,8,15,18-22,24,26]
- No difference[16,17,23,25,27]
- Rescue atropine requirements
  - No difference[6,15-18,25]

Reactive Hypertension
- No difference[6,16,19,21-23]

Vomiting
- No difference[6,8,16-26]
- Higher in PE group*[15,27]

Cardiac Output
- No difference[19,20,27]
- Higher in NE group*[24]

Systemic Vascular Resistance
- No difference[19,20,27]
- Higher in PE group*[24]

*$p < .05$

Neonatal

Apgar Scores
- No difference[6,8,15-27]

Lactate Levels
- No difference[16,18,20,24,26]

Umbilical Artery Blood Gas
- No difference in pH, pO_2, pCO_2[6,8,15,16,18,20,22-26]
- Base deficit higher in NE group*[26]

Glucose Levels
- No difference[16,20]
- Higher in NE group*[18,24]

*$p < .05$

Potency Equivalency & Dose-Finding

Phenylephrine vs. Norepinephrine Dose Equivalency

ED	Phenylephrine	Norepinephrine	Potency
ED 50[29]	137 mcg*[29]	10 mcg*[29]	13.1:1[29]
ED 90[30]	90.9 mcg*[30]	8 mcg*[30]	11.4:1[30]

Norepinephrine (mcg/kg)[31]

ED 50	ED 95
0.067 mcg/kg*	0.121 mcg/kg*

Norepinephrine (mcg/kg/min)

ED 50	ED 80ǂ/ED90♦	ED 95
0.042 mcg/kg/min*[32]		0.097 mcg/kg/min*[32]
0.029 mcg/kg/min*[33]	0.080 mcg/kg/min♦*[33]	
0.029 mcg/kg/min*[34]	0.068 mcg/kg/minǂ*[34]	0.105 mcg/kg/min*[34]

*95% CI, SAIH during cesarean section

Limitations

- Single-center studies[6,8,15-27] → difficult to generalize
- Elective cesarean section[6,16-21,23-27]
- Gravid patients without severe comorbidities[6,15-21,23-27]
- NE and PE doses may not have been equipotent[18,22,27]

Recommendations

For adult parturients undergoing cesarean section requiring SA

Crystalloid Bolus	• Pre-load or co-load • 500-1,000 mL
NE Infusion Dose	• 0.05 mcg/kg/min or 2.5-3.5 mcg/min • Titrate to SBP within 90-110% of baseline
Initiation of Infusion	• Time of SA injection • Discontinue based on adequate BP
Acute Hypotension	• Additional 3-10 mcg NE boluses

Future Research

- NE use in patients with pre-eclampsia
- Application to other surgeries requiring SA
- NE benefits in non-gravid populations
- Potency equivalencies between NE and PE

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Institutional Review Board approval was not required for this research project.