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## SCIENTIFIC ARTICLE

# Effect of equipotent doses of bupivacaine and ropivacaine in high-fat diet fed neonatal rodent model

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### KEYWORDS

Bupivacaine;  
Ropivacaine;  
Intrathecal  
anesthesia;  
Spinal toxicity;  
Obesity

### Abstract

**Objectives:** The increase in the prevalence of obesity presents a significant health and economic problem. Obesity has been reported to be a major contributor to variety of chronic diseases. Childhood obesity has been rising over the past decades leading to various complications in health. Millions of infants and children undergo surgery every year on various health grounds. The present investigation was undertaken to evaluate the effect of spinal anesthesia of equipotent doses of ropivacaine and bupivacaine on over-weight neonatal rats.

**Methods:** The Sprague-Dawley rat pups were overfed on high fat diet to induce obesity. Behavioral assessments for sensory and motor blockade was made by evaluating thermal and mechanical withdrawal latencies at various time intervals following intrathecal injections of bupivacaine (5.0 mg/kg) and ropivacaine (7.5 mg/kg) in P14 rats. Spinal tissue was analyzed for apoptosis by determination of activated caspase-3 using monoclonal anti-activated caspase-3 and Fluoro-Jade C staining. Long-term spinal function in P30 rat pups was evaluated.

**Results:** Exposure to intrathecal anesthesia in P14 increased thermal and mechanical latencies and was observed to increase apoptosis as presented by increase in activated caspase-3 and Fluoro-Jade C positive cells. Significant alterations in spinal function were observed in high fat diet-fed pups as against non-obese control pups that were on standard diet. Bupivacaine produced more pronounced apoptotic effects on P14 pups; ropivacaine however produced long lasting effects as evidenced in motor function tests at P30.

**Conclusion:** Ropivacaine and bupivacaine induced spinal toxicity that was more pronounced in over-fed rat pups as against normal controls.

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## PALAVRAS-CHAVE

Bupivacaína;  
Ropivacaína;  
Anestesia intratecal;  
Toxicidade medular;  
Obesidade

## Efeito de doses equipotentes de bupivacaína e ropivacaína em modelo de roedor neonatal alimentado com dieta rica em gordura

### Resumo

**Objetivos:** O aumento da prevalência da obesidade é um problema sério de saúde e econômico. A obesidade tem sido relatada como um dos principais contribuintes para uma variedade de doenças crônicas. A obesidade infantil tem aumentado nas últimas décadas, levando a várias complicações de saúde. Milhões de bebês e crianças são submetidos à cirurgia todos os anos por diversos motivos de saúde. O presente estudo foi realizado para avaliar o efeito da raquianestesia com doses equipotentes de ropivacaína e bupivacaína em ratos recém-nascidos com sobrepeso.

**Métodos:** As crias de ratos Sprague-Dawley foram sobrealimentados com dieta rica em gordura para induzir obesidade. Avaliações comportamentais para bloqueio sensorial e motor foram feitas através da avaliação das latências de retirada térmica e mecânica em vários intervalos de tempo após injeções por via intratecal de bupivacaína (5,0 mg/kg) e ropivacaína (7,5 mg/kg) em ratos P14. Tecido medular foi analisado para apoptose por determinação da caspase-3 ativada, usando anticorpo monoclonal anti-caspase 3 ativada e coloração com Fluoro-Jade C. A função da coluna vertebral a longo prazo em filhotes de ratos P30 foi avaliada.

**Resultados:** A exposição à anestesia intratecal em P14 aumentou as latências térmica e mecânica e foi observado que aumentou a apoptose, como apresentado pelo aumento da caspase-3 ativada e células positivas para Fluoro-Jade C. Alterações significativas da função da coluna vertebral foram observadas em filhotes alimentados com dieta rica em gordura versus filhotes controles não-obesos em dieta padrão. Bupivacaína produziu efeitos apoptóticos mais pronunciados sobre os filhotes P14; ropivacaína, entretanto, produziu efeitos duradouros como evidenciado nos testes de função motora em P30.

**Conclusão:** Ropivacaína e bupivacaína induziram toxicidade medular mais pronunciada nos filhotes de ratos sobrealimentados que nos controles normais.

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## Introduction

Childhood obesity is one of the most serious public health challenges of the 21st century. The prevalence of childhood obesity has increased at an alarming rate. Obesity affects around 1.5 billion people around the globe today<sup>1,2</sup> of which 200 million are children.<sup>3</sup> Obese and over-weight children have higher chances of developing obesity-related complications.<sup>4,5</sup>

Obesity has also been reported to be associated with several surgical pathologies.<sup>6</sup> The physiological changes in obesity markedly affect distribution, binding, and elimination of anesthetic drugs<sup>7-9</sup> and severe adverse reactions could possibly result if drug dosing is based only on the actual body weight of the patient.

Regional anesthesia as combined spinal-epidural anesthesia or integrated epidural and light general anesthesia are often employed in obese patients to lessen the risks related to airway control and postoperative respiratory depressions that are induced by general anesthetics or opioids used in treatment of pain.<sup>10</sup>

Bupivacaine is used as a local anesthetic that is employed in nerve block, epidural, and intrathecal anesthesia and is often administered to control pain before, during and after spinal surgery.<sup>11</sup> Although extensively used in pain control, bupivacaine has been reported to be cardiotoxic, neurotoxic, and is the most myotoxic of the local anesthetics.<sup>12</sup>

Ropivacaine, an aminoamide derivative is a local anesthetic drug that is structurally related to mepivacaine and bupivacaine, and has therapeutic properties similar to those of bupivacaine but associated with less motor blockade and toxicity.<sup>13</sup> In clinical studies, ropivacaine appears to be suitable for both epidural and regional anesthesia.<sup>14</sup> The present study was undertaken to study the effects of bupivacaine and ropivacaine in over-weight/obese neonatal rats.

## Materials and methods

### Animals

This study was approved by the Medical Ethics Committee of the First People's Hospital of Jining, institutional animal care committee and was performed in accordance with the National Institutes of Health Guide for the Use of Laboratory Animals. The pregnant female Sprague-Dawley rats (Guangdong Medical Laboratory Animal Co., China) were used. The rats were housed in a room on a 12 h light/dark cycle with free access to water. The animals were housed individually in separate cages and monitored closely for the day of birth, which was considered as postnatal day 0 (P0). The rat pups (male and female) were kept in cages in a room on a 12 h light/dark cycle with free access to water with their littermates till P5. Neonatal overfeeding was done to induce

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