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SCIENTIFIC ARTICLE

# Subarachnoid meloxicam does not inhibit the mechanical hypernociception on carrageenan test in rats☆

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**KEYWORDS**
NSAIDs;
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**Abstract**
*Background and objective:* Evaluate the antinociceptive effects of subarachnoid meloxicam on the mechanical hypernociception induced by carrageenan in rats.
*Methods:* Randomized controlled trial. Eighteen adult male Wistar rats underwent a cannula implantation into the subarachnoid space and were randomly divided into two groups: Group I received saline solution 5 μL, while Group II received meloxicam 30 mg. The mechanical hypernociception was induced by intraplantar injection of carrageenan and evaluated using a digital analgesy meter every 30 min during a 4-h period. The results were recorded as the Δ withdrawal threshold (in g), calculated by subtracting the measurement value after treatment from baseline.
*Results:* The Δ withdrawal threshold mean values were lower in the group of patients treated with meloxicam over all time points between 45 and 165 min, however, there was no statistical significance ($p = 0.835$) for this difference.
*Conclusion:* Subarachnoid meloxicam at a dose of 30 μg animal$^{-1}$ did not suppress the mechanical hypernociception in a model of inflammatory pain induced by intraplantar administration of carrageenan in rats. The data suggest that other dosages should be investigated the drug effect is discarded.


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**PALAVRAS-CHAVE**
AINE;
Carragenina;
Dor;
Medula espinhal

**Meloxicam subaracnoide não inibe a hipernocicepção mecânica no teste da carragenina em ratos**

**Resumo**
*Justificativa e objetivo:* avaliar os efeitos antinociceptivos do meloxicam subaracnóideo sobre a hipernocicepção mecânica induzida pela carragenina em ratos.
*Métodos:* estudo randômico e controlado. Dezoito ratos Wistar, machos adultos, foram submetidos à implantação de uma cânula subaracnóidea, e aleatoriamente distribuídos em dois grupos: o Grupo I (GI) recebeu 5 μL de solução salina, enquanto que ao Grupo II (GII) foram administrados 30 μg de meloxicam, ambos pela via subaracnóidea. A hipernocicepção mecânica foi induzida pela injeção intraplantar de carragenina e avaliada com o emprego de um analgesímetro digital a cada 30 minutos durante um período de 4 horas. Os resultados foram registrados como o Δ do limiar de retirada (g), calculado subtraindo-se o valor das mensurações após os tratamentos, do valor basal.
*Resultados:* os valores médios do Δ do limiar de retirada foram menores no grupo tratado com meloxicam ao longo de todos os momentos de avaliação entre 45 e 165 minutos, contudo não foi demonstrada significância estatística (p = 0,835) para essa diferença.
*Conclusão:* a administração subaracnóidea do meloxicam na dose de 30 μg.animal$^{-1}$ não foi capaz de suprimir a hipernocicepção mecânica em um modelo de dor inflamatória induzida pela administração intraplantar de carragenina em ratos. Os dados sugerem que outras doses sejam pesquisadas antes que o efeito do fármaco seja descartado.


## Introduction

Evidence has shown that besides the known peripheral action nonsteroidal anti-inflammatory drugs (NSAIDs) have a powerful effect on experimental pain that is independent of its anti-inflammatory effects.[1] In addition to its peripheral inhibition of prostaglandin synthesis, a central action of NSAIDs has been suggested by experimental studies in which these drugs demonstrated greater potency by subarachnoid administration compared to systemic administration.[2,3] Studies have shown that both cyclooxygenase (COX) forms are constitutively expressed in the brain and spinal cord of rats,[4] with COX-2 the predominant isoform in the spinal cord dorsal horn.[5] Spinal administration of anti-inflammatory drugs has shown to suppress the reflection of C fibers, inhibit neuronal sensitization in the spinal cord dorsal horn, and attenuate long-term inflammatory pain.[2,6–11]

Meloxicam is an analgesic and nonsteroidal anti-inflammatory drug, which belongs to the phenolic acid class and has a preference for COX-2 isoenzyme.[12] Unlike many other NSAIDs, it has high oral bioavailability and a long half-life, although not free from side effects.[13] Studies of meloxicam administered by spinal pathways are scarce[14–17] and do not assess its effects on acute inflammatory pain. The aim of this study was to evaluate the antinociceptive power of subarachnoid meloxicam on acute pain induced by carrageenan in rats.

## Materials and methods

The experimental protocol was reviewed and approved by the Animal Experimentation Ethics Committee of the institution. Rats were individually housed under controlled temperature (21–24 °C) and light–dark cycle of 12 h, with food and water ad libitum offered for at least 14 days.

The animals were surgically prepared under anesthesia with intraperitoneal injections of ketamine and xylazine (100 and 10 mg kg$^{-1}$, respectively); then, a cannula was implanted in the subarachnoid space, according to a modification of the technique previously described in the literature.[18] Briefly, the animals were placed in prone position, with the fore and hind limbs fixed in abduction and the region of the head slightly elevated relative to the rest of the body. After skin antisepsis of atlantooccipital region, a vertical incision approximately 2 cm in length was made in the region midline, starting at the point between the ears and extending caudally. The subcutaneous tissue and *biventer cervicis* and *rectus capitis dorsalis* major muscles were removed by blunt dissection. With the muscular retraction, the dura and *cisterna magna* were seen, and after exposure of atlantooccipital membrane, an 18 G needle was used to puncture its central region, until cerebrospinal fluid is seen. A PE-10 polyethylene cannula (#BB31695-PE/1, Scientific Commodities, Lake Havasu City – AZ, USA) was then inserted through the hole and advanced caudally 8.5 cm into the subarachnoid space until it reaches the lumbar enlargement region. Measuring, cutting, and marking of cannulas with enamel paint were conducted prior to the experiment period, with this material individually packaged and sterilized with ethylene oxide. The cranial portion of the cannula was inserted through an 18 G needle, allowing its accommodation in the subcutaneous tissue, in order to emerge from the skin near the top of the head. Muscles and skin were sutured and the catheter external end was occluded with the insertion of a small fragment of dental needle