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Review Article

The role of pharmacotherapy in modifying the neurological status of patients with spinal and spinal cord injuries☆

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ABSTRACT

The aim here was to conduct a review of the literature on pharmacological therapies for modifying the neurological status of patients with spinal cord injuries. The PubMed database was searched for articles with the terms "spinal cord injury AND methylprednisolone/GM1/apoptosis inhibitor/calpain inhibitor/naloxone/tempol/tirilazad", in Portuguese or in English, published over the last five years. Older studies were included because of their historical importance. The pharmacological groups were divided according to their capacity to interfere with the physiopathological mechanisms of secondary injuries. Use of methylprednisolone needs to be carefully weighed up: other anti-inflammatory agents have shown benefits in humans or in animals. GM1 does not seem to have greater efficacy than methylprednisolone, but longer-term studies are needed. Many inhibitors of apoptosis have shown benefits in *in vitro* studies or in animals. Naloxone has not shown benefits. Tempol inhibits the main consequences of oxidation at the level of the spinal cord and other antioxidant drugs seem to have an effect superior to that of methylprednisolone. There is an urgent need to find new treatments that improve the neurological status of patients with spinal cord injuries. The benefits from treatment with methylprednisolone have been questioned, with concerns regarding its safety. Other drugs have been studied, and some of these may provide promising alternatives. Additional studies are needed in order to reach conclusions regarding the benefits of these agents in clinical practice.

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O papel da farmacoterapia na modificação do estado neurológico de traumatizados vértebro-medulares

Palavras-chave:
Traumatismos da medula espinal
Metilprednisolona

RESUMO

O objetivo deste trabalho foi fazer uma revisão da literatura sobre a terapia farmacológica para a modificação do estado neurológico de traumatizados vértebro-medulares. Foi feita uma na base de dados Pubmed por artigos com os termos "spinal cord injury AND

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Gangliosídeo G(M1)
Apoptose
Calpaína
Naloxona

methylprednisolone/GM1/apoptosis inhibitor/calpain inhibitor/naloxone/tempol/tirilazad", em português ou em inglês, publicados nos últimos cinco anos. Trabalhos mais antigos foram incluídos pela sua importância histórica. Os grupos farmacológicos foram divididos em função da sua capacidade para interferir nos mecanismos fisiopatológicos da lesão secundária. O uso de metilprednisolona deve ser cuidadosamente ponderado. Outros anti-inflamatórios mostraram benefícios em humanos ou em animais. O GM1 não aparenta ter maior eficácia do que a MP, mas estudos em mais longo prazo são necessários. Muitos inibidores da apoptose têm mostrado benefício em estudos *in vitro* ou em animais. A naloxona não deu mostras de benefício. O tempol inibe as principais consequências da oxidação no nível da medula e outros fármacos antioxidantes aparentam ter um efeito superior ao da metilprednisolona. É urgente encontrar novos tratamentos que melhorem o estado neurológico dos traumatizados vértebro-medulares. Os benefícios do tratamento com metilprednisolona têm sido questionados, há preocupações em relação à sua segurança. Outros fármacos têm sido estudados, podem alguns deles ser opções promissoras. Estudos adicionais são necessários para tirar conclusões sobre o benefício desses agentes na prática clínica.

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Introduction

Spinal and spinal cord injuries are among the most devastating traumatic situations and are responsible for high morbidity and mortality rates. The consequences of these injuries include reduction of motor and sensory capacity and perturbations of intestinal, urinary and sexual functioning.[1] The impact of these problems becomes greater through absence of satisfactory therapy for modifying these patients' neurological status.[1]

The pathogenesis of spinal cord injuries can be divided into two phases. The primary injury occurs immediately, and is characterized by compression, bruising or, rarely, complete breakage of the spinal cord. The secondary lesions arise over the course of several days and involve a variety of processes, such as inflammation, edema, ischemia, hemorrhage, electrolytic imbalances, release of arachidonic acid, excitotoxicity due to glutamate, apoptosis and lipid peroxidation. These phenomena lead to expansion of the primary lesion and cavitation of the spinal cord.[1,2] Pharmacological therapies for spinal and spinal cord injuries have the aim of inhibiting these processes or stimulating spinal cord regeneration.

Methylprednisolone (MP), which is frequently used in treating acute spinal cord injuries, showed evidence of benefits in the National Acute Spinal Cord Injury Survey (NASCIS) II and NASCIS III studies.[3,4] However, these findings have not been reproduced in other studies and use of MP is becoming increasingly controversial, because of the risk of potentially serious complications, in comparison with the modest benefits.[1] This has led to efforts toward developing new drugs that might improve neurological functioning in cases of these diseases.[1]

The objective of this study was to conduct a review of the literature on pharmacological therapy for spinal and spinal cord injuries.

Materials and methods

A search for articles was conducted in the PubMed database, using the terms "spinal cord injury AND methylprednisolone/GM1/apoptosis inhibitor/calpain inhibitor/naloxone/tempol/tirilazad", in Portuguese or in English, published over the last five years. Some older studies were also included because of their historical importance.

The pharmacological groups were divided according to their capacity for interfering in the physiopathological mechanisms of secondary lesions.

Drugs that inhibit inflammation

Subsequent to spinal and spinal cord injury, inflammation and hydrolysis occur in the spinal cord, which results in destruction of neurons and microvessels.[4] The main function of these drugs is to inhibit or modify the local inflammatory response.

Methylprednisolone

MP is the best known and most studied anti-inflammatory drug for attempting to block this process, and thus forms the paradigm.

The NASCIS studies proposed to administer MP at high doses (loading dose of 30 mg/kg of weight and maintenance dose of 5.4 mg/kg/h), for 24 h if the treatment was started not more than 3 h after the injury, or for 48 h if it was started between 3 and 8 h after the injury.[3,4]

In victims of complete cervical rupture, increased levels of interleukin (IL) 6, IL-8, macrophage chemoattractant protein-1, neutrophil activating peptide-2, intercellular adhesion molecule-1 (ICAM-1), soluble Fas, tissue inhibitors of metalloproteinase-1 and matrix metalloproteinases (MMP) 2 and 9 have been observed.[5] Treatment with MP after spinal

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