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SYSTEMATIC REVIEW OF RECOVERY OF SPINAL CORD INJURY WITH ANTIOXIDANT THERAPY

REVISÃO SISTEMÁTICA DA RECUPERAÇÃO DE TRAUMA RAQUIMEDULAR COM TERAPIA ANTIOXIDANTE

REVISIÓN SISTEMÁTICA DE RECUPERACIÓN DE TRAUMA RAQUIMEDULAR CON TERAPIA ANTIOXIDANTE

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ABSTRACT

The objective of the paper is to analyze the frequency and efficacy of experimental studies with antioxidant therapy. A search was conducted in the pubmed.gov database using the keywords "antioxidants" AND "spinal cord injury", from January 2000 to December 2015, resulting in 686 articles. Studies of non-traumatic injuries, non-antioxidant therapies, absence of neurological and functional evaluation, and non-experimental studies were excluded, leaving a total of 43 articles. The most used therapies were melatonin (16.2%), quercetin (9.3%), epigallocatechin and edaravone (6.9%). The most frequent route of administration was intraperitoneal (72.09%). The dose and mode of administration varied greatly, with a single dose being the most commonly used (39.53%). The time elapsed from trauma to treatment was 0-15 minutes (41.8%), 15-60 minutes (30%) and over 60 minutes (10.6%). Histological analysis was performed in 32 studies (74.41%). The BBB scale was the main functional measure applied (55.8%), followed by the inclined plane test (16.2%) and the Tarlov scale (13.9%). Positive outcomes were observed in 37 studies (86.04%). The heterogeneity of antioxidant therapy, with different types, doses, and measurements observed, limits the comparison of efficacy. Standardized protocols are required to make clinical translation possible.

Keywords: Antioxidants; Spinal cord injuries; Neurology; Neurosurgery; Review.

RESUMO

O objetivo do presente estudo é analisar a frequência e a eficácia dos estudos experimentais com terapia antioxidante. Realizou-se uma pesquisa na base de dados pubmed.gov usando as palavras-chave "antioxidants" (antioxidantes) AND "spinal cord injury" (trauma raquimedular), de janeiro de 2000 a dezembro de 2015, resultando em 686 artigos. Estudos de lesões não traumáticas, terapias não antioxidantes, ausência de avaliação neurológica e funcional e estudos não experimentais foram excluídos, restando 43 artigos. As terapias mais utilizadas foram melatonina (16,2%), quercetina (9,3%), epigalocatequina e edaravona (6,9%). A via de administração mais frequente foi intraperitoneal (72,09%). A posologia e o modo de administração tiveram grande variação, sendo que a dose única foi a forma mais frequente (39,53%). O tempo decorrido desde o trauma até a instituição do tratamento foi de 0 a 15 minutos (41,8%), 15 a 60 minutos (30%) e acima de 60 minutos (10,6%). A análise histológica foi realizada em 32 estudos (74,41%). O sistema de escala BBB foi a principal medida funcional aplicada (55,8%), seguida de teste com plano inclinado (16,2%) e a escala de Tarlov (13,9%). Os desfechos positivos foram observados em 37 estudos (86,04%). A heterogeneidade da terapia antioxidante com diferentes tipos, doses e medições observadas limita a comparação da eficácia. Protocolos padronizados são necessários para tornar possível a tradução clínica.

Descritores: Antioxidantes; Traumatismos da medula espinal; Neurologia; Neurocirurgia; Revisão.

RESUMEN

El objetivo del presente estudio es analizar la frecuencia y eficacia de los estudios experimentales con terapia antioxidante. Se realizó una búsqueda en la base de datos pubmed.gov utilizando las palabras clave "antioxidants" (antioxidantes) AND "spinal cord injury" (trauma raquimedular), de enero de 2000 a diciembre de 2015, y se encontraron 686 artículos. Se excluyeron los estudios de lesiones no traumáticas, terapias no antioxidantes, con ausencia de evaluación neurológica y funcional y los estudios no experimentales, quedando 43 artículos. Las terapias más utilizadas fueron melatonina (16,2%), quercetina (9,3%), epigalocatequina y edaravona (6,9%). La vía de administración más común fue intraperitoneal (72,09%). La dosificación y administración fueron variadas, pero la dosis única fue la forma más frecuente (39,53%). El tiempo trascurrido desde el trauma a la iniciación del tratamiento fue de 0-15 minutos (41,8%), 15 a 60 minutos (30%) y más de 60 minutos (10,6%). El análisis histológico se realizó en 32 estudios (74,41%). El sistema de la escala BBB se aplicó como la principal medición funcional (55,8%), seguida por la prueba del plano inclinado (16,2%) y la escala de Tarlov (13,9%). Se observaron resultados positivos en 37 estudios (86,04%). La heterogeneidad de la terapia antioxidante con diferentes tipos, dosis y mediciones observados limita la comparación de la eficacia. Son necesarios protocolos estandarizados para tornar posible la traducción clínica.

Descriptores: Antioxidantes; Traumatismos de la médula espinal; Neurología; Neurocirugía; Revisión.

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INTRODUCTION

Spinal cord injury (SCI) can occur by traumatic or ischemic event. Following the primary injury, cellular necrosis and tissue degeneration are the secondary events, caused mainly by hypoxia and ischemia.[1,2] A reduction in blood flow and microvascular abnormalities were demonstrated, leading to an increase in intracellular free radical species.[3,4] Lipid peroxidation of the cell membrane has a novel role in the pathophysiology of neuronal lesion.[2]

There is no effective treatment to prevent the secondary damage caused by SCI.[5] Corticosteroids were used to reduce edema formation and inflammatory events, with controversial results.[3,6-9] Investigations to find a specific therapy to control the formation of free radicals are ongoing.[10] The role of antioxidant drugs and hyperbaric oxygenic therapy is also being discussed.[11,12]

There are many publications that focus on antioxidant treatment after SCI, with different neurological outcomes. The present study analyzes the various types of antioxidant drugs used in experimental SCI, in order to define the most common and effective ones.

MATERIALS AND METHODS

A literature review was carried out in the database *pubmed.gov*, on December 13, 2015, using the keywords "antioxidants" AND "spinal cord injury", without filters. The selection of keywords was based on MeSH terms structure. The papers included were *in vivo* SCI studies treated by antioxidant therapy from January 2000 to December 2015. A total of 686 articles were found, which were then reviewed by two independent observers, considering the exclusion criteria reported in Figure 1. Full text PDFs of potentially relevant articles were obtained, in order to better select the articles.

The inclusion criteria were: experimental study in rats with SCI treated with antioxidant drugs and followed up to verify functional recovery. Articles in English, Spanish or Portuguese were included. The exclusion criteria were: lack of abstract, therapies other than antioxidant therapy, studies in animals other than rats, review articles, epidemiological or case-report studies, and lack of neurological and histological assessment.

The variables analyzed in the selected papers were: (I) year of publication, (II) type of the antioxidant drug used, (III) mechanism of action, (IV) posology, (V) administration form, (VI) elapsed time between the trauma and the treatment, and (VII) assessment of motor recovery and histology.[13-55] (Table 1)

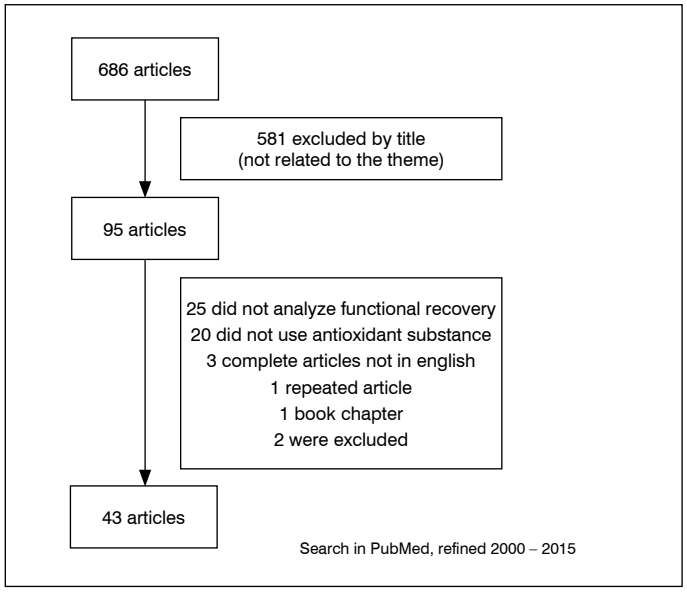

Figure 1. Flowchart. The search resulted in 686 articles. After applying the exclusion and inclusion criteria, 43 papers remained.

The year of publication was shown as a frequency graph, and the annual publication rate was determined by Pearson's Correlation and Simple Linear Regression, obtaining the slope ("b" coefficient). For both, statistics, the software program SPSS Statistics v. 24 for Mac (IBM, New York, USA) was used. Significance was defined as $p<0.05$.

"The study was a review and systematic analysis of scientific articles published on PubMed. In this case, there was no need for prior authorization by an ethics committee, as the works selected for the study were expressly authorized by their respective ethics committees. This study reviewed and analyzed these publications, and there was no contact with or prospective or retrospective data on animals or patients in any phase."

RESULTS

Paper selection and inclusion

Initially, 686 articles were retrieved. After analyzing each paper and applying the inclusion and exclusion criteria, forty-three articles were included in the study. (Figure 1)

The studies were reported according to the year of publication on PubMed: 2000-2004 (5 articles, 11.6%), 2005-2009 (13 articles, 30.2%), and 2010-2015 (25 articles, 58.1%). A mean of 3.6 papers were published per year. There was a significant increase in the number of publications in past 15 years (slope= 0.33, r= 0.69, p= 0.012). (Figures 2 and 3)

Antioxidant therapy

The most common drug used was melatonin (7 articles, 16.2%), followed by quercetin (4 articles, 9.3%), epigallocatechin (3 articles, 6.9%), and edaravone (3 articles, 6.9%). The most frequent administration route was intraperitoneal in 31 papers and oral or nasogastric tube in 8 papers. (Table 1)[13]- The posology and frequency showed wide variation that did not depend on the type of drug administered. Most of the articles used one dose only (17 articles, 39.5%), more than 7 doses (9 articles, 20.9%) and two doses (6 articles, 13.9%).

The elapsed times from SCI to treatment was 0-15 minutes (18 articles, 41.8%), 15 to 60 minutes (13 articles, 30%), and after 1 hour (5 articles, 10.6%). (Table 2) One study was classified separately because the treatment was started 5 minutes before SCI. Six papers (13.9%) did not specify the time of drug administration after SCI. Eighteen studies started treatment immediately after SCI.

Functional recovery

Basso, Bresnahan and Beattie (BBB scale system) was used to perform the functional measurement in 24 articles (55.8%). The following tests were inclined plane test (16.2%) and Modified Tarlov Scale (13.9%).

Histology was performed to analyze the efficacy in 32 articles (74.41%).

Time of observation

The follow-up time of the animal was less than one week (14 articles, 32.5%), 2 weeks (6 articles, 13.9%), 3 weeks (8 articles, 18.6%), 4 weeks (8 articles, 18.6%) and more than 4 weeks (5 articles 11.6%) (Table 1). Two articles do not report the follow-up time. (Table 2)

Outcomes

Positive outcomes were observed in 37 papers (86%) after antioxidant treatment.

Negative outcomes were observed in 6 studies (13.9%). Two papers with negative outcomes started treatment immediately after trauma, using melatonin and agmatine as antioxidant therapy.

Table 1. Papers included in the study.

Author	Antioxidant theraphy	Mechanism of action	Posology	Administration mode	Elapsed time from SCI to therapy	Functional recovery measurement
Cemil, et al. (2012)[13]	Aged Garlic Extract	Antioxidant proprieties, molecular mechanism uncertain	250 mg/kg	Oral	24 hour	Inclinated Plane Test, Histology
Kotil, et al. (2006)[14]	Agmatine	Inhibits enzime iNOS	50 mg/kg ou 100mg/kg	Intraperitoneal	5 minutes	Tarlov Neurological Scale, Inclinated Plane Test
Toklu, et al. (2010)[15]	Alpha-Lipoic Acid	Co-factor for several mitochondrial dehydrogenases, participates in redox reactions.	50 mg/kg	Intraperitoneal	30 minutes	Gale Motor Fuctional Scale, Histology
Sayin, et al. (2013)[16]	Alpha-Lipoic Acid		50, 100, 150, 200 mg/kg	Intraperitoneal	Immediately	BBB†, Inclinated Plane Test, Histology
Al Jadid, et al. (2009)[17]	Alpha-Tocopherol	Endogenous antioxidant and reduces lipid peroxidation and generation of free radicals	1000mg/kg and 2000mg/kg	Oral	Not Specified	Behavior Test
Asirvatham, et al. (2012)[18]	Alpha-Tocopherol		2,000 mg/kg	Intraperitoneal	Not Specified	BBB†
Soy, et al. (2004)[19]	Aminoguanidine	High-potency iNOS inhibitor	100mg/kg	Intraperitoneal	Immediately	Inclinated Plane Test, Tarlov Neurological Scale, Histology
Moon, et al. (2012)[20]	Angelica Dahuricae	Inhibits LPS- induced expression of inflammatory mediators such as NO, inducible nitric oxide synthase (iNOS), COX-2, and TNF-alpha in macrophages by inhibiting MAPKsand IkB/NF-kB signal pathways.	100mg/kg	Oral	2 hour	Inclinated Plane Test, Foot Print Test, Histology
Kim, et al. (2011)[21]	Anthocyanin	As antioxidant efects, inhibit inflammation, as a scavenger of active oxygen species	400 mg/kg	Via NG-tube	Not Specified	BBB†, Histology
Zhang, et al. (2014)[22]	Apigenin	Anti-oxidant through inhibition of NADPH-oxidase enzyme	10 mg/kg and 20 mg/kg	Intraperitoneal	Immediately	BBB†
Impellizzeri, et al. (2011)[23]	Apocynin		5mg/kg 10% DMSO	Intraperitoneal	1 hour	Neurological Examination, Histology
Yan, et al. (2014)[24]	Ascorbic Acid	Free Radical Scavenger	100mg/kg 200mg/kg	Intraperitoneal	1 hour	BBB†, Foot Print Test, Histology
Wang, et al. (2014)[25]	Curcumin	Inhibition of NF-kB and JAK2/ STAT3 pathways, decreases levels of IL-1 e NO.	50mg/kg	Intraperitoneal	Not Specified	BMS Scale, Histology
Kim, et al. (2014) [26]	Curcumin		200mg/kg	Intraperitoneal	Not Specified	BBB†, Histology
Kalayci, et al. (2005)[27]	Ebselen	Glutatione-related mechanism, still uncertain	10mg/kg	Intraperitoneal	Immediately	Inclinated Plane Test, Neurological Examination, Histology
Ozgiray, et al. (2011)[28]	Edaverone	Inhibitory effect on lipid peroxidation by scavenging free radicals, and it prevents vascular endothelial cell injury	3 mg/kg	Intraperitoneal	1 hour	Tarlov Neurological Scale
Wang, et al. (2013)[29]	Edaverone		5mg/kg	Intraperitoneal	5 minutes	BBB†, Histology
Otha, et al. (2005)[30]	Edaverone		5mg/kg	Endovenous	5 minutes	BBB†, Histology
Khalatbary, et al. (2009) [31]	Epigallocatechin Gallate	Act in inflammation and apoptosis, uncert	50/kg	Intraperitoneal	Immediately	Behavior Test, Histology
Tian, et al. (2013)[32]	Epigallocatechin Gallate		20mg/kg	Intrathecal	Immediately	BBB†, Histology
Genovese, et al. (2007)[33]	Melatonin	Free radical scavenger, stimules catalase, SOD, GSH- reductase, peroxidase. Decreases lipid peroxidation.	10mg/kg	Intraperitoneal	1 hour	BBB†, Histology
Schiaveto-de-Souza, et al. (2013)[34]	Melatonin		2.5mg/kg	Intraperitoneal	5 min prior SCI and 1h after	BBB†
Park, et al. (2012)[35]	Melatonin		10 mg/kg	Subcutaneous	24 hour	BBB†
Gul, et al. (2005)[36]	Melatonin		50mg/kg; 100mg/kg	Intraperitoneal	Immediately	Inclinated Plane Test, Neurological Examination, Histology
Genovese, et al (2005)[37]	Melatonin		50mg/kg	Intraperitoneal	30 minutes	Tarlov Neurological Scale, Histology
Cayli, et al. (2004)[38]	Melatonin		10mg/kg	Intraperitoneal	Immediately	Gale Motor Fuctional Scale, Eletrophysiology
Fujimoto, et al. (2000)[39]	Melatonin		2,5mg/kg	Intraperitoneal	5 minutes	Tarlov Neurological Scale, Inclinated Plane Test, Histology
Fee, et al. (2010)[40]	Melatonin Analogue		10mg/kg and 100mg/kg	Intraperitoneal	15 minutes	Behavior Test, Histology

Table 1. Papers included in the study.

Author	Antioxidant theraphy	Mechanism of action	Posology	Administration mode	Elapsed time from SCI to therapy	Functional recovery measurement
Liu, et. Al. (2013)[41]	Mn (III) Tetrakis	Potentializes SOD activity and scavengers ROS	4 mg/kg	Intrathecal	Immediately	BBB†, Histology
Hillard, et al. (2004)[42]	Tempol	Stimulate SOD catalytic activity, also inhibits hydroxyl radical generation by oxidizing transition metals necessary for Haber-Weiss/Fenton reactions.	69mg/kg, 138mg/kg, 275mg/kg, 550mg/kg	Intraperitoneal	20 minutes	BBB†, Histology
Ling, et al. (2013)[43]	Mn (III) Tetrakis	Potentializes SOD activity and scavengers ROS	10mg/kg	Intraperitoneal	1 hour	Histology
Cavus, et al. (2014)[44]	Montelukast	Leukotrien receptor antago- nist that specifically inhibites sodium cisteinyl leukotrien CysLT1 receptor, diminishing inflammatory process	5mg/kg	Intraperitoneal	Immediately	Tarlov Neurological Scale, Histology
Kanter, et al. (2006)[45]	Nigella Sativa	Anti-inflammatory, immunomodulatory	0,2ml/kg	Intraperitoneal	Immediately	Inclinated Plane Test, Neurological Examination, Histology
Assis, et al. (2014)[46]	Proantrocyanidin	Stimulates SOD, inhibits NDMA glutamate receptors	10/mg/kg	Intraperitoneal	1 hour	BBB†, Grip Force Test
Schultke, et al. (2010)[47]	Quercitin	Scavenger, decreases lipid peroxidation	25mmol/kg	Intraperitoneal	1 hour	BBB†, Histology
Song, et al. (2013)[48]	Quercitin		0,2mg/kg	Intraperitoneal	1 hour	BBB†, Histology
Schultke, et al. (2003)[49]	Quercitin		5, 25, 50, 100 mmol/kg	Intraperitoneal	1 hour	BBB†, Histology
Genovese, et al. (2006)[50]	Quercitin		30mg/kg	Oral	1 hour	BBB†, Histology
Ates, et al. (2006)[51]	Resveratrol	Anti-oxidation effect, suppression of immunoreactivity, reduction of inflammatory cytokines including IL-1β, IL-10, TNF-α, and myeloperoxidase, inhibition of injury-induced apoptosis	100mg/kg	Intraperitoneal	24h	Motor Function Score, Inclinated Plane Test, Histology
Liu, et. Al. (2011)[52]	Resveratrol		200mg/kg	Intraperitoneal	Not Specified	BBB†, Behavior Test,Locomotor Rating Scale, Histology
Yune, et al. (2009)[53]	Scutellaria Baicalensis	Inhibition lipopolysaccharide-induced expression and anti-inflammatory proprieties	30, 100, or 300 mg/kg	Oral	2 hour	BBB†, Footprint Test, Histology
Sharma, et al. (2006)[54]	Sintetic (H-29051)	Melatonin Analogue	50mg/kg	Via NG-tube	10 minutes	Inclinated Plane Test, Histology
Serarslan, et al. (2010)[55]	Tadalafil	Aa selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5	2 mg/kg	Via NG-tube	Immediately	Neurological Examination

Papers included and variables analyzed. † BBB (Basso, Bresnahan and Beattie scale system).

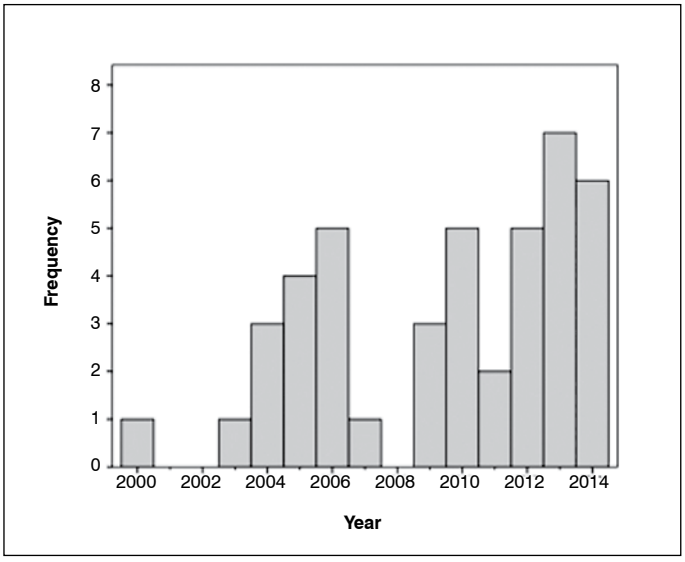

Figure 2. Frequency. The articles were divided by year of publication.

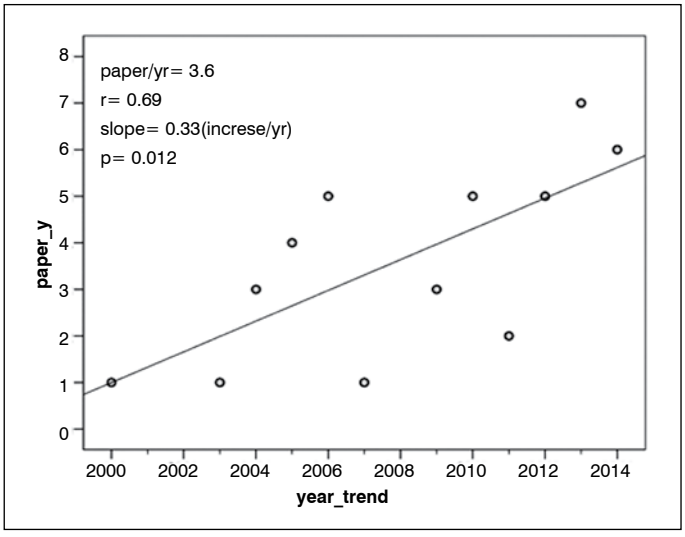

Figure 3. Statistical analysis. Pearson's Correlation and Linear Regression were used to obtain the slope.

Table 2. Variables observed in the study.

Variable	Number of articles	%
Antioxidant		
Melatonin	7	16.2
Quercitin	4	9.3
Epigalloccatecin	3	6.9
Edaverone	3	6.9
Resveratrol	2	4.6
Curcumin	2	4.6
Alpha-Licoic Acid	2	4.6
Other*	20	46.5
Administration mode		
Intraperitoneal	31	72
Oral/Nasogastric Tube	8	18.6
Intrathecal	2	4.6
Subcutaneous	1	2.3
Intravenous	1	2.3
Total dosage		
1 Dose	17	39.5
2 Doses	6	13.9
3 Doses	3	6.9
4 Doses	2	4.6
5 Doses	1	2.3
7 Doses	4	9.3
> 7 doses	9	20.9
Functional recovery		
BBB†	24	55.8
Inclinated Plain Test	7	16.2
Modified Tarlov Scale	6	13.9
Other	6	13.9
Elapsed time trauma to therapy		
0-15 minutes	18	41.8
15 min - 30 min	3	6.9
30 min - 60 min	10	23.2
> 60 min	5	11.6
Not Specified	6	13.9
Time of observation		
< 1 week	14	32.5
1 week - 2 weeks	6	13.9
2 weeks - 3 weeks	8	18.6
3 weeks - 4 weeks	2	4.6
4 weeks	6	13.9
> 4 weeks	5	11.6
Not specified	2	4.6

The variables studied and its frequencies are resumed in this table. *Other type of antioxidant are presented in Table 1. † BBB (Basso, Bresnahan and Beattie scale system).

DISCUSSION

After SCI, the inflammatory response occurs by cellular activation in order to reorganize the damaged tissue. This process increases the intensity and the volume of the lesion. Antioxidant therapy seeks to minimize the cellular effects of hypoxia and ischemia, leading to a better functional outcome after trauma.[1-4] The present study showed better outcomes in 37 studies (86%) where antioxidant therapy was used after experimental SCI. The most common therapy was the use of melatonin by the intraperitoneal route immediately after trauma.

Antioxidants are subdivided into two categories based on their hydrophilic or hydrophobic characteristics. Hydrophilic substances interact with intracellular enzymes, reducing reactive species production in the mitochondrial system by chemical reduction. Hydrophobic substances protect the cell membranes from damage.

Hypoxia secondary to SCI leads to free radical formation and lipid peroxidation, whereby lipids from plasmatic and intracellular membranes are converted by reactive species into malondialdehyde, leading to destruction of the membrane structure. This disarrangement of the intracellular membranes leads to activation of apoptosis, culminating in neuronal damage, with loss of motor, sensitive and autonomic functions, or even death.[56,57] Antioxidant therapy blocks this cascade by scavenging free radicals and inhibiting different enzymes, such as superoxide-dismutase, glutathione peroxidase and catalase.[12]

Number of doses and start of treatment

Eight papers had an incomplete or partial description of the methods used; they did not specify the number of doses given (n= 6) or time treatment was started (n= 2). This information is essential to analyze its efficacy and verify which drug is the best for a clinical trial.

It was difficult to analyze the efficacy of antioxidant therapy because of the different method and types of drugs used. Starting therapy before trauma was not clinically relevant. Five articles started the treatment 1 hour after trauma, making clinical translation possible.

Analysis of functional recovery

The majority of the articles (28 papers, 82.3%) completed the analysis of functional recovery at 3 weeks. It is known that the inflammatory process is reduced slowly and gradually. There is evidence to support the hypothesis that 4 weeks is the minimum time needed to analyze the histological and functional recovery.[58] An analysis period of less than 4 weeks is insufficient to correctly determine the response to the treatment.

The limitations of the study were missing information, the different types of antioxidant therapy, the different doses, and different times elapse between the trauma and the start of therapy. The present article is the most complete and up-to-date review of antioxidant therapy in SCI.

As future perspectives, the research group will design an in vivo experimental study to analyze the efficacy of antioxidant therapy after SCI, to provide evidence for clinical translation.

FINAL REMARKS

The literature shows heterogeneity of antioxidant treatment with different types, doses, measurements that limit the comparison of efficacy. Standardized protocols for antioxidant therapy need to be designed to make the clinical translation viable.

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AOSpine Latin America

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