UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA:
CIÊNCIAS MÉDICAS

Trauma Raquimedular: Aspectos Epidemiológicos, de Recuperação Funcional e de Biologia Molecular.

Marcelo de Mello Rieder

Porto Alegre

2014

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Trauma Raquimedular: Aspectos Epidemiológicos, de Recuperação Funcional e de Biologia Molecular.

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"Tratar com desigualdade a iguais, ou a desiguais com igualdade, seria desigualdade flagrante, e não igualdade real.”

(Rui Barbosa.)

Resumo

Introdução: O Traumatismo Raquimedular (TRM) é um evento catastrófico súbito e inesperado que traz consequências drásticas nos âmbitos de saúde e social de um indivíduo. Os estudos que avaliam as causas e recuperação funcional de TRM no nosso meio são escassos. Não há estudos que utilizem o emprego de biomarcadores séricos como prognosticadores da recuperação funcional. Os objetivos deste estudo são: descrever as Causas das Lesões Medulares de um hospital especializado em trauma na cidade de Porto Alegre e comparar com outros centros no Brasil; avaliar as taxas de mortalidade, tempo de ventilação mecânica, tempo de internação destes pacientes; avaliar e funcionalidade mediante o emprego da MIF no momento da alta e 6 meses após a lesão medular; avaliar os Niveis Séricos dos Biomarcadores: Neuronio Específico Enolase, Irterleucina-6, e Fator Neurotrófico Derivado das Celulas Gliais em pacientes com Trauma Raquimedular Isolado; avaliar o comportamento destes Biomarcadores nas primeiras 48 horas e comparar com o grupo controle, correlacionando as alterações clínicas e o prognóstico nos pacientes com TRM.

Material e Métodos: Estudo de coorte prospectivo com pacientes com TRM de várias etiologias. Foram incluídos no estudo todos os pacientes que sobreviveram de TRM isolado que foram atendidos no nosso hospital Cristo Redentor no período de 2010 a 2013. Devido ao considerável número de pacientes com TRM devido a lesões por arma de fogo, estudamos prospectivamente a reabilitação funcional deste grupo de pacientes. Durante a hospitalização, todos os pacientes foram submetidos a uma intensiva reabilitação e a mesmo continuou após a alta hospitalar. Foram avaliadas as escalas da American Spinal Injury Association (ASIA) e a Medida de Indepencência Funcional (MIF) no momento a alta hospitalar e após 6 meses de lesã. Ainda, foram estudados biomarcadores da fase aguda da lesão com objetivo de entender melhor a fisiopatologia das lesões medulares e pesquisar marcadores de prognóstico nesses pacientes.

Resultados: A Coorte foi composta de 81 pacientes com média (DP) de 32.6 (±12.2) anos, sendo 76 (93.8%) homens. Na nossa coorte, lesão por arma de fogo foi a maior causa de TRM (x%), enquanto que TRM em acidente de trânsito foram obersvadas em x% e as provocadas por quedas em x%. Os pacientes com TRM causado por lesão por arma de fogo apresentaram menor grau de comprometimento na escala ASIA motora de membro superior, em função de estas lesões afetarem mais porções mais caudais da medula. Entretanto, não observamos diferenças na MIF entre os grupos. Após seis

meses, os pacientes apresentaram uma significativa melhora nas escalas ASIA e MIF. O grau de melhora foi similar nas lesões causadas por arma de fogo e de outras etiologias. Nas 48 horas após o TRM observamos elevação significativa de interleucina 6 (IL-6) e enolase neurônio-específica (NSE). No entanto, essa elevação não pôde ser correlacionada com a causa, tipo, severidade da lesão ou prognóstico dos pacientes.

Conclusôes: As lesões por arma de fogo são importantes causas de TRM e déficits neurológicos no nosso meio, sendo essse cenário possivelmente reflexo da panorama do TRM no Brasil. A recuperação funcional do TRM severo provocado por armas de fogo é pequena, mas similar aos traumas provocados por queda e acidentes automobilísticos. Nas primeiras 48 horas IL-6 e NSE aumentam significativamente nesses pacientes, embora esse amento não tenha uma correlação clínica mais direta.

Palavras-Chave: Recuperação Funcional, Fisioterapia, Trauma Raquimedular Agudo, Biomarcadores.

Abstract

Introduction: The Spinal Cord Injury (SCI) is a sudden and unexpected catastrophic event that brings drastic consequences in the areas of health and welfare of an individual. Studies assessing the causes and functional recovery of TRM in our environment are lacking in literature. No studies using the employment of serum biomarkers as predictors of functional recovery. The objectives of this study are to describe the Causes of Spinal Injuries of a specialized trauma hospital in the city of Porto Alegre and compare with other centers in Brazil. We assessed the rates of mortality, duration of mechanical ventilation and length of stay of these patients and evaluated the functionality through the use of the FIM at discharge and 6 months. We also evaluated levels of serum biomarkers : Neuron Specific Enolase , Interleukin -6 - Derived Neurotrophic Factor and Glial Cells from patients with Spinal Cord Trauma Isolated and the behavior of these biomarkers in the first 48 hours and compared with the control group correlating the clinical findings and prognosis in patients with SCI .

Material and Methods: Prospective cohort study conducted in patients with severe TSCI with different etiologies. All survivals patients of isolated acute TCSI who were attended in our center from 2010 to 2013 were included in this study. Patients were divided in two groups if TSCI, those with lesions provoked by firearms was provoked by firearm or other causes. During hospitalization all patients were submitted to intensive rehabilitation and followed in a rehabilitation program after discharge. They were evaluated with ASIA and FIM at the time of the hospital discharge and six mounts latter. Sorological biomarkers were evaluated in the first 48 hours.

Results: The cohort was composed by 81 patients, mean age (±S.D.) of 32.6 (±12.2) years, being 76 (93.8%) males. Patients with TSCI caused by firearms showed lower degree of impairment than other patients in ASIA motor superior, because a larger number of patients in the group of firearm lesions showed lumbar woods. However, in the other scales we did not observed this difference. After six months, patients showed significant improvement in ASIA and FIM scales. The degree of improvement was similar between patients with TSCI caused by firearms or others. There was an increase of biomarkers IL-6, NSE and GDNF.

Conclusions: TSCI provoked by firearms are an important cause of spinal lesion and neurological deficits in Brazil. Functional recovery in severe TSCI provoked by firearms is limited but similar than severe TSCI provoked by falls or automobilist accidents.
Key words: Functional Recovery, Physiotherapy, Acute Firearm Spinal Cord Injuries, Biomarkers

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Lista de Abreviaturas

AVC	Acidente Vascular Cerebral
ASIA	*American Spinal Injury Association*
FDA	Food and Drug Administration
GFAP	Glial Fibrilary acidic protein
GDNF	Glial Cell Line-derived Neurotrophic Factor
IL-6	Interleucina 6
IL-8	Irterleucina 8
LCR	Liquido cefalorraquidiano
MBP	Myelin Basic Protein,
MIF	Medida de Independência Funcional
MV	Mechanical Ventilation
NFL	Neurofilament Protein
NSE	Neuron Especific Enolase
NT	Não Testada
NSCID	National Spinal Cord Injury Database
PESS	Potenciais Evocados Somato-Sensitivos
TRM	Traumatismo Raquimedular
TCE	Traumatismo Cranioencefálico
TNF	Tumor Necrosis Factor
TSCI	Traumatic Spinal Cord Injury
ZPP	Zona de Preservação Parcial

Nota: Várias siglas foram mantidas conforme a língua inglesa, bem como a sua definição, por serem assim conhecidas universalmente.

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1 - INTRODUÇÃO

1 - Introdução Geral

O Traumatismo Raquimedular (TRM) é um evento catastrófico súbito e inesperado que traz consequências drásticas nos âmbitos de saúde e social de uma pessoa. É caracterizado por comprometimentos da motricidade, sensibilidade superficial e profunda e distúrbios neurovegetativos dos segmentos do corpo localizados abaixo do nível da lesão. (1, 2)

O TRM incide predominantemente em pacientes de 18 a 40 anos, do sexo masculino, e as principais etiologias traumáticas são variáveis de acordo com a região estudada. No Brasil, a epidemiologia do TRM não é completamente conhecido e tem sido relativamente pouco estudada. Estima-se que acidentes de trânsito, ferimentos por arma de fogo e quedas ou mergulhos sejam as principais causas. (3, 4)

De acordo com o *National Spinal Cord Injury Database* (NSCID), a lesão da medula espinhal é definida como a ocorrência de uma lesão traumática aguda dos elementos do canal medular (medula espinhal ou cauda equìna), resultando na perda temporária ou permanente sensitiva e/ou motora. (5)

A definição clínica de lesão medular, para o NSCID, exclui as doenças do disco intervertebral, as lesões vertebrais na ausência de lesão medular, as avulsões de raízes nervosas, as lesões de nervos periféricos e de raízes nervosas fora do canal medular, o câncer, as doenças vasculares da medula espinhal e outras doenças medulares não traumáticas. Essencialmente, as lesões traumáticas envolvem um

evento e um mecanismo externo mais evidente do que uma doença degenerativa. (6)

2 – REVISÃO DE LITERATURA

2.1 - Estratégias para Selecionar e Organizar Informações

Nessa revisão de literatura abordamos alguns aspectos da fisiopatologia do TRM.

A estratégia de busca envolveu as seguintes bases de dados: MEDLINE (*site* Pubmed), LILACS, SCIELO, Biblioteca Brasileira de Tese e Dissertações, Portal Domínio Público e Portal Cochrane.

As referências bibliográficas dos artigos identificados foram revisadas para localizar outras não contempladas na busca. Nos sites MEDLINE, LILACS, SCIELO foram realizadas buscas com as palavras- chave.

Foram realizadas buscas e cruzamentos através dos termos *"spinal cord injury", "funcional recovery", "firearms", "trauma" e "spinal cord injury", "funcional recovery", "trauma", "biomarkers"*. Após arrolagem inicial dos estudos foi aplicada uma filtragem, selecionando os estudos em humanos, publicados nos últimos 5 anos e nos seguintes delineamentos: revisões sistemáticas e ensaios clínicos.

Figura 1. Estratégias de busca sobre as bases que fundamentam esta Tese.

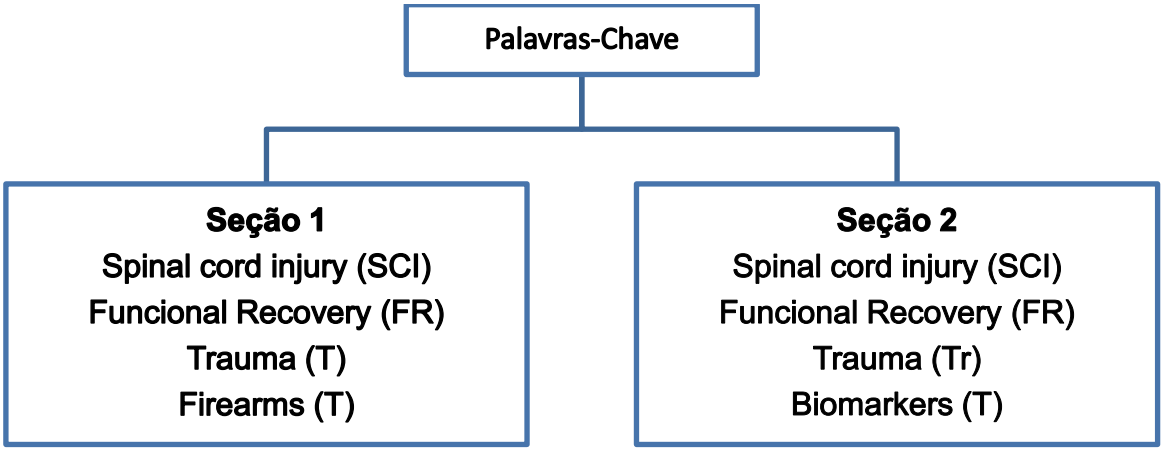


Figura 2. Estratégias de busca sobre as bases que fundamentam a primeira seção.

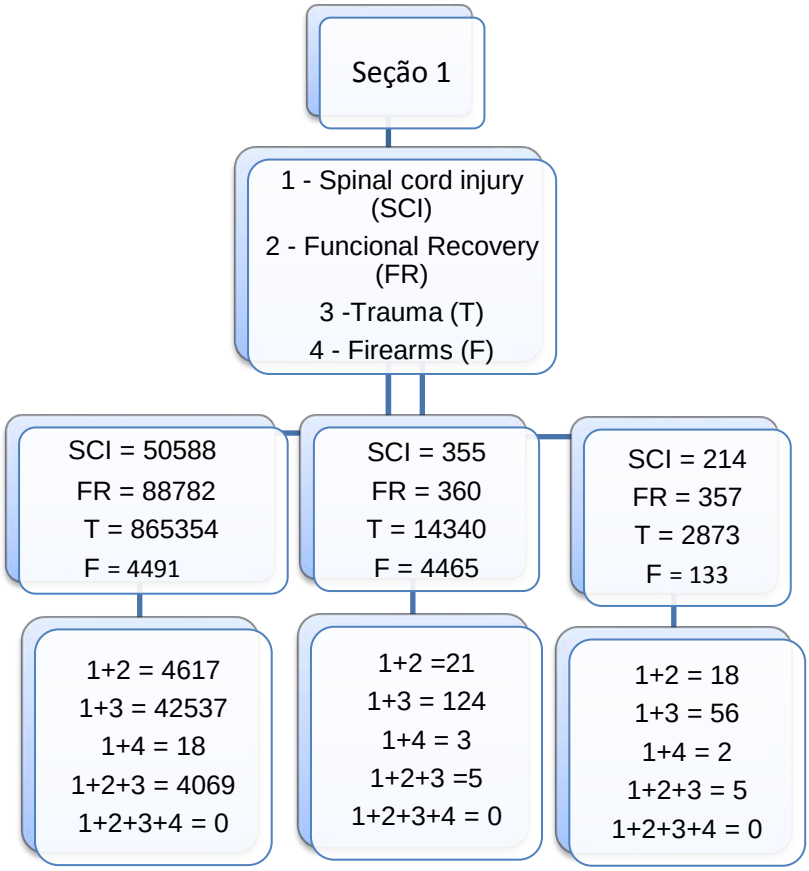
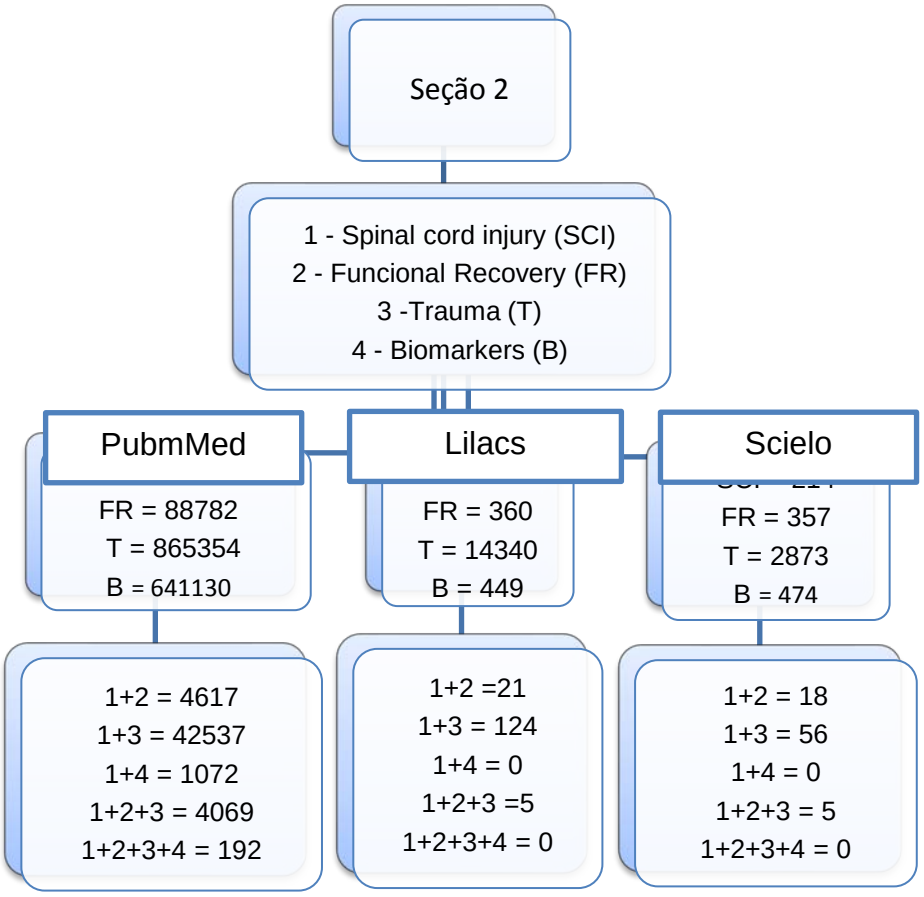


Figura 3. Estratégias de busca sobre as bases que fundamentam a segunda seção.



2.2 – Epidemiologia

O conhecimento da prevalência e incidência das lesões traumáticas da medula espinhal é importante em função dos altos impactos pessoais, biológicos e psicológicos, assim como as altas consequências sócio-econômicas a curto e longo prazo. A diversidade etiológica das lesões traumáticas também enfatiza a necessidade de investimento em programas de prevenção primária e secundária. (7)

A incidência global de lesão é estimada em 23 casos por milhão, com aproximadamente 179.312 casos novos por ano. Alguns dados regionais disponíveis classificam a América do Norte com 40 casos/milhão de habitantes, Oeste Europeu com 16 casos/milhão de habitantes, e Australia com 15 casos/milhão de habitantes. Dados extrapolados estão disponíveis para Asia-Central 25 casos/milhão de habitantes, Sul da Ásia 21 casos/milhão de habitantes, Caribe 19 casos/milhão de habitantes e América Latina 25 casos/milhão de habitantes. No continente africano a incidência é estimada em 29 casos/milhão de habitantes (3,8-10).

As informações sobre indivíduos com TRM não são inteiramente conhecidas. Isso é mais especialmente verdadeiro para os países em desenvolvimento e isso tem dificultando a prevenção dessas lesões, os cuidados de saúde e de planejamento social.(8).

No Brasil estima-se em mais de 11 mil vítimas de TRM isolado anualmente, acometendo nove homens para cada mulher. A média de idade das vítimas é de 30,4 ± 15,5 anos. O coeficiente de incidência de lesão medular no Brasil é estimado em 71 novos casos por milhão de habitantes por ano. A região Nordeste apresentou a incidência mais elevada, com 91 casos/milhão de habitantes. Ela é seguida pela região Centro-Oeste, com 79 casos/milhão de habitantes, Sudeste com 71 casos/milhão de habitantes registrados. As regiões Norte e Sul apresentam as mais baixas incidências, com 49 e 38 casos/milhão de habitantes, respectivamente. Em cada região, as causas mais frequentes são os acidentes de trânsito, seguidos de mergulhos, quedas e perfurações por arma de fogo (9).

Os custos com a lesão medular são altíssimos. Isso se deve ao alto grau de sequela neurológica e também psicológica em pacientes que ainda estão em idade

profissional produtiva. Estima-se que o custo de um paciente tetraplégico, ao longo do resto de sua vida, possa chegar a meio milhão de dólares (10, 11).

2.3 - Fisiopatologia

A transferência de energia cinética para a medula espinhal, o rompimento dos axônios, a lesão das células nervosas e a ruptura dos vasos sanguíneos causam a lesão primária da medula espinhal. A fisiopatologia da lesão medular traumática envolve a compreensão de dois mecanismos, ou momentos, de lesão: a primária e a secundária (6, 12).

Lesão Primária: A lesão primária é a resultante do trauma mecânico inicial e pode ser compreendida como a combinação do impacto inicial com uma eventual compressão subsequente. Tem relação direta e imediata com o trauma. O dano medular direto é resultante da transferência da energia cinética para a medula espinhal e pode ocorrer por meio de quatro mecanismos básicos: o estiramento, a laceração, a compressão e a secção. Tal trauma determina dano nos axônios, nas células gliais e nos vasos sanguíneos em diferentes graus (parcial ou completo). O único meio de evitar a lesão primária e impedir a ocorrência do trauma só pode ser obtido com medidas preventivas (13).

Lesão Secundária: A evidência apresentada para apoiar a teoria da lesão secundária é a hipótese de que um mecanismo-chave é a isquemia pós-traumática com infarto resultante da medula espinhal, envolvendo hipóxia, desvios iônicos intracelulares, excitocidade neuronal, produção de eicosanóides, produção de radicais livres, peroxidação de lipídeos, desacoplamento da produção de energia e do metabolismo celular e apoptose neuronal (13, 14).

A evidência para o papel dos mecanismos vasculares tem sido obtida por uma variedade de modelos de lesão medular aguda em várias espécies. Muitos métodos diferentes angiográficos foram utilizados para avaliar a microcirculação da medula e para medir o fluxo sanguíneo da medula espinhal após o trauma. Com estas técnicas, os principais efeitos sistêmicos e locais de lesão vascular aguda da medula espinal foram identificados e envolvidos na etiologia da lesão secundária (15).

Os efeitos sistêmicos da lesão medular aguda incluem hipotensão e redução do débito cardíaco. Os efeitos locais incluem a perda de auto-regulação no segmento lesado da medula espinal e uma acentuada redução da microcirculação, especialmente na região hemorrágica e nas zonas adjacentes (16).

A perda da microcirculação se estende por uma distância considerável proximal e distal ao local da lesão. Muitos estudos têm mostrado uma redução dose-dependente do fluxo sangüíneo medular variando com a gravidade da lesão, o que piora com o tempo após a lesão (10).

Os déficits funcionais devido à lesão aguda da medula espinal foram medidos eletrofisiologicamente. Os efeitos histológicos incluem necrose hemorrágica precoce levando a infarto importante no local da lesão. Estes efeitos vasculares pós-traumáticos podem ser tratados (10, 17).

2.4 - Apresentações Clínica

Os mecanismos básicos das lesões no TRM são a fratura ou a fratura e luxação. Metade das lesões ocorre na coluna cervical, um sexto na região torácica e um terço na região lombossacra. O trauma é a causa mais comum da síndrome de

transecção da medula espinal. Uma hemissecção da medula (Síndrome de Brown-Sequard) é rara e normalmente associada à lesão penetrante por projétil ou faca (**Tabelas 1 e 2**) (18).

Tabela 1: Síndromes Clínicas no TRM

Síndrome Centro-Medular	Lesão que ocorre quase exclusivamente na região cervical, com preservação da sensibilidade sacra e maior debilidade dos membros superiores que dos membros inferiores.
Síndrome de Brown-Sequard	Esta lesão é caracterizada por: perda ipsilateral da função motora e propriocepção; perda contralateral da sensibilidade à dor e à temperatura.
Síndrome de Transecção da Medular	Abaixo do nível da lesão, o paciente perde a motricidade, a sensibilidade e os reflexos autonômicos (inclusive os esfincterianos).
Síndrome Anterior Medular	Lesão que produz perda da função motora e da sensibilidade à dor e à temperatura, preservando a propriocepção.
Síndrome do Cone Medular	Lesão da medula sacra (cone) e das raízes lombares dentro do canal, que usualmente resulta em arreflexia de bexiga, intestino e membros inferiores. Os segmentos sacros podem ocasionalmente mostrar reflexos preservados, por exemplo, o bulbocavernoso e os reflexos miccionais.
Síndrome da Cauda Equina	Lesão das raízes nervosas lombossacras dentro do canal neural resultando em arreflexia de bexiga, intestino e membros inferiores.

Tabela 2: Termos Usados nas Lesões de Medula

Tetraplegia	Descreve a diminuição ou perda da função motora e/ou sensitiva dos segmentos cervicais devido à lesão dos elementos neurais dentro do canal medular. A tetraplegia resulta em diminuição da função dos membros superiores, tronco, membros inferiores e órgãos pélvicos. Não inclui lesões do plexo braquial ou dos nervos periféricos fora do canal vertebral.
Paraplegia	Descreve a diminuição ou perda da função motora e/ou sensitiva dos segmentos torácicos, lombares ou sacrais (porém não cervicais), secundários a danos dos elementos neurais dentro do canal vertebral. A paraplegia deixa íntegros os membros superiores; contudo, dependendo do nível, pode incluir tronco, membros inferiores e órgãos pélvicos. O termo é corretamente usado para descrever lesões da cauda equina e do cone medular, porém não lesões do plexo lombossacral ou lesões de nervos periféricos fora do canal.
Tetraparesia ou Paraparesia	O uso desses termos não é recomendado, já que descrevem lesões incompletas de maneira imprecisa. No entanto, a Escala de Avaliação da American Spine Injury Association (ASIA) oferece um enfoque mais preciso.
Dermátomo	Refere-se à área da pele inervada por axônios sensitivos dentro de cada nervo segmentar (raiz).
Miótomo	Refere-se ao grupo de fibras musculares inervadas pelos axônios motores dentro de cada nervo segmentar (raiz).
Nível	Refere-se ao segmento mais distal da medula espinhal com função

Neurológico	motora e sensitiva normal em ambos os lados do corpo.
Nível Sensitivo	Refere-se ao segmento mais distal da medula que tem função sensitiva normal em ambos os lados do corpo.
Nível Motor	Refere-se ao segmento mais distal da medula que tem função motora normal em ambos os lados do corpo.
Nível Esquelético	Refere-se ao nível em que se encontra, por meio do exame radiológico, o maior dano vertebral.
Índice Sensitivo e Índice Motor	Soma numérica que reflete o grau de deficiência neurológica associado com a lesão medular.
Lesão Incompleta	Se for encontrada preservação parcial da função sensitiva e/ou motora abaixo do nível neurológico, incluindo o segmento sacral mais baixo, a lesão se define como incompleta. A sensibilidade sacra inclui sensação na região da união cutâneo-mucosa perianal, assim como a sensação anal profunda. A prova da função motora é a presença de contração voluntária do esfíncter anal externo ao exame digital.
Lesão Completa	Esse termo é usado quando houver ausência da função motora e sensitiva no segmento sacral mais baixo.
Zona de Preservação Parcial (ZPP)	Refere-se àqueles dermátomos e miótomos distais ao nível neurológico que permanecem parcialmente inervados. Quando se encontra alguma alteração da função sensitiva e/ou motora abaixo do segmento normal mais baixo, o número exato desses segmentos deve ser anotado para ambos os lados como ZPP. O termo é usado somente em lesões completas.

2.5 - Avaliações Clínica

O exame neurológico consiste na avaliação da sensibilidade, da função motora e dos reflexos. A área de sensibilidade do paciente é examinada no sentido craniocaudal, desde a região cervical, pela avaliação da sensibilidade à variação de temperatura, sensibilidade dolorosa e sensibilidade tátil, que são funções mediadas pelo trato espinotalâmico lateral, cujas fibras estão na porção anterolateral da medula espinhal (19, 20).

A avaliação da vibração por meio de diapasão ou da posição espacial dos membros avalia as condições do trato posterior da medula espinhal (funículo grácil e cuneiforme). A distribuição dos dermátomos possui importância semiológica relacionada ao nível da lesão, como os mamilos (T4), processo xifóide (T7), umbigo (T10), região inguinal (T12-L1) e região perineal (S2-S3-S4).

A avaliação da função motora avalia as condições dos tratos corticoespinhais e tem como objetivo a determinação do grau de movimento que o paciente possui. Deve ser quantificado com relação ao grau de força muscular, determinada por meio de uma escala que varia de 0 a 5. A paralisia total é considerada 0; a presença de contração muscular palpável ou visível, 1; a presença de movimento ativo, mas que não vence a força da gravidade, 2; movimento ativo que vence a força da gravidade, 3; movimento ativo que vence alguma resistência, 4 e movimento ativo normal, 5 (21-23,25)

A Associação Americana do Trauma Raquimedular (ASIA- American Spine Injury Association) desenvolveu, em 1992, padrões para a avaliação e classificação neurológica do TRM, avaliação que apresenta, no momento, grande aceitação em nível mundial (Figura 1). A avaliação neurológica é baseada na sensibilidade e na

função motora, e possui uma etapa compulsória, baseada na qual é determinado o nível da lesão neurológica, o nível motor e o nível sensitivo, obtendo-se números que, em conjunto, fornecem um escore. A outra etapa consiste na avaliação da sensibilidade profunda e superficial (24).

O exame da sensibilidade é realizado por meio da pesquisa dos 28 dermátomos de ambos os lados, atribuindo-se uma avaliação numérica de acordo com o achado clínico: 0- ausente,1- alterada, 2- normal e NT (não testada) quando, por qualquer motivo, a avaliação do dermátomo não puder ser realizada. O esfíncter anal externo deve ser também examinado por meio da introdução do dedo do examinador no orifício anal, com a finalidade de determinar se a lesão é completa ou incompleta (sensibilidade presente-sim, ou ausente-não) (21-23)

A avaliação da função motora é realizada por meio da avaliação, de ambos os lados, de músculos denominados “músculos chaves” em 10 pares de miótomos, sendo a força muscular graduada de 0 a 5. Os músculos selecionados para a avaliação e os níveis neurológicos correspondentes são:

C5- flexores do cotovelo

C6- flexores do punho

C7- extensores do cotovelo

C8- flexores do dedo (falanges média e distal)

T1- abdutores (dedo mínimo)

L2- flexores do quadril

L3- flexores do joelho

L4- dorsiflexores do tornozelo

L5- extensor longo dos dedos

S1- flexores plantares do tornozelo

A avaliação da deficiência é baseada na Escala de Frankel, modificada pela ASIA, que consiste em 05 graus de incapacidade (20):

a) lesão completa - não existe função motora ou sensitiva nos segmentos sacrais S4-S5; b) lesão incompleta - preservação da sensibilidade e perda da função motora abaixo do nível neurológico, estendendo-se até os segmentos sacrais S4-S5; c) lesão incompleta – a função motora é preservada abaixo do nível neurológico, e a maioria dos músculos chaves abaixo deste nível possui grau menor ou igual a 3; d) lesão incompleta – a função motora é preservada abaixo do nível neurológico e a maioria dos músculos chaves abaixo deste nível possui grau maior ou igual a 3; e) normal – sensibilidade e força motora preservadas (25, 26).

O diagnóstico clínico do Trauma Raquimedular é baseado em sintomas clínicos neurológicos e mais recentemente, em exames de imagens, especialmente tomografia computadorizada e ressonância magnética. A ressonância magnética convencional é a melhor imagem para a avaliação na fase aguda. Entretanto, em muitos locais e serviços de saúde não existe a possibilidade da realização deste exame e, mesmo quando possível, a instabilidade clínica do paciente não permite a realização do mesmo (27).

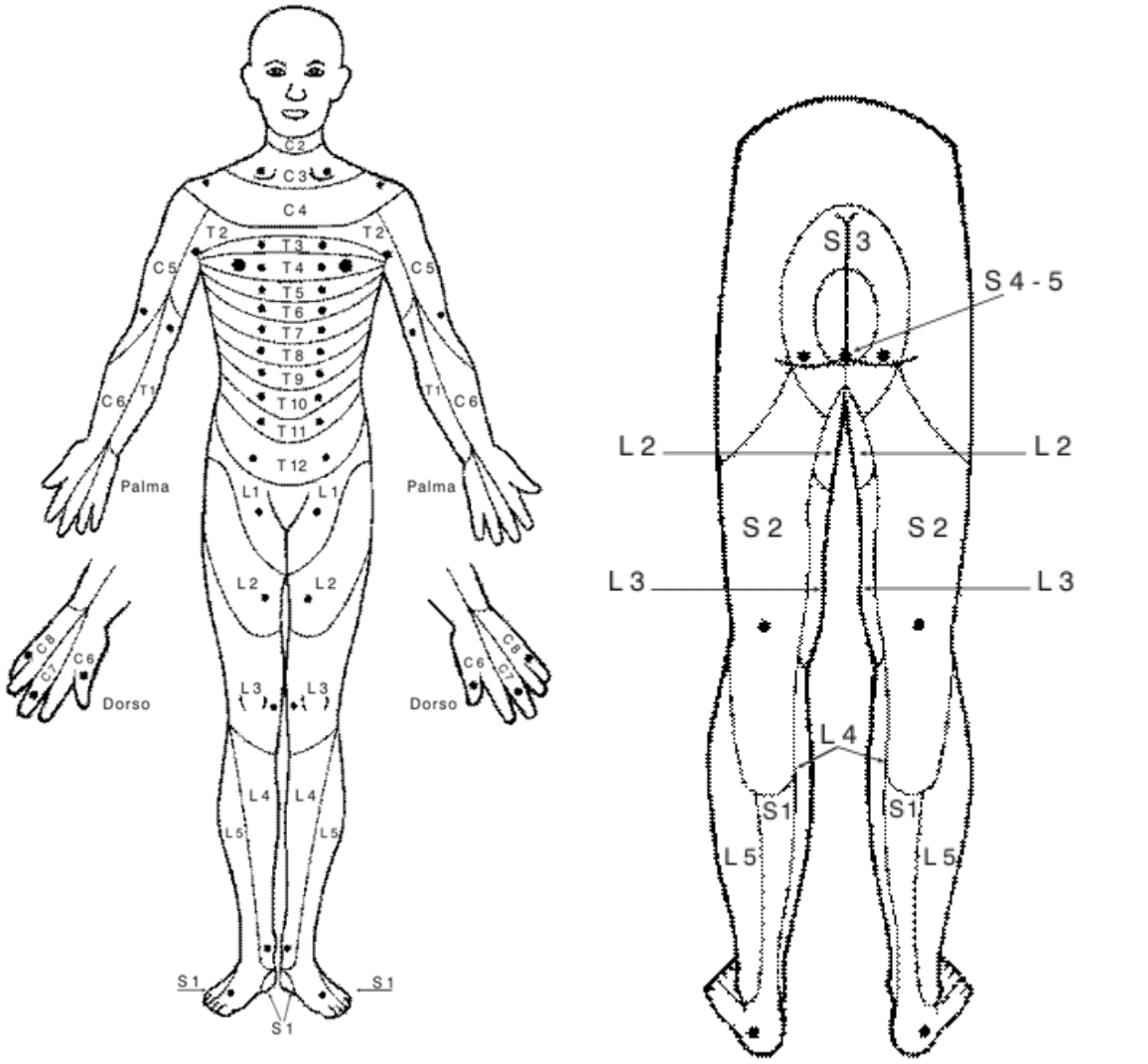


Figura 4: Distribuição dos Dermátomos do Membro Superior, Membro Inferior e Região Perineal.

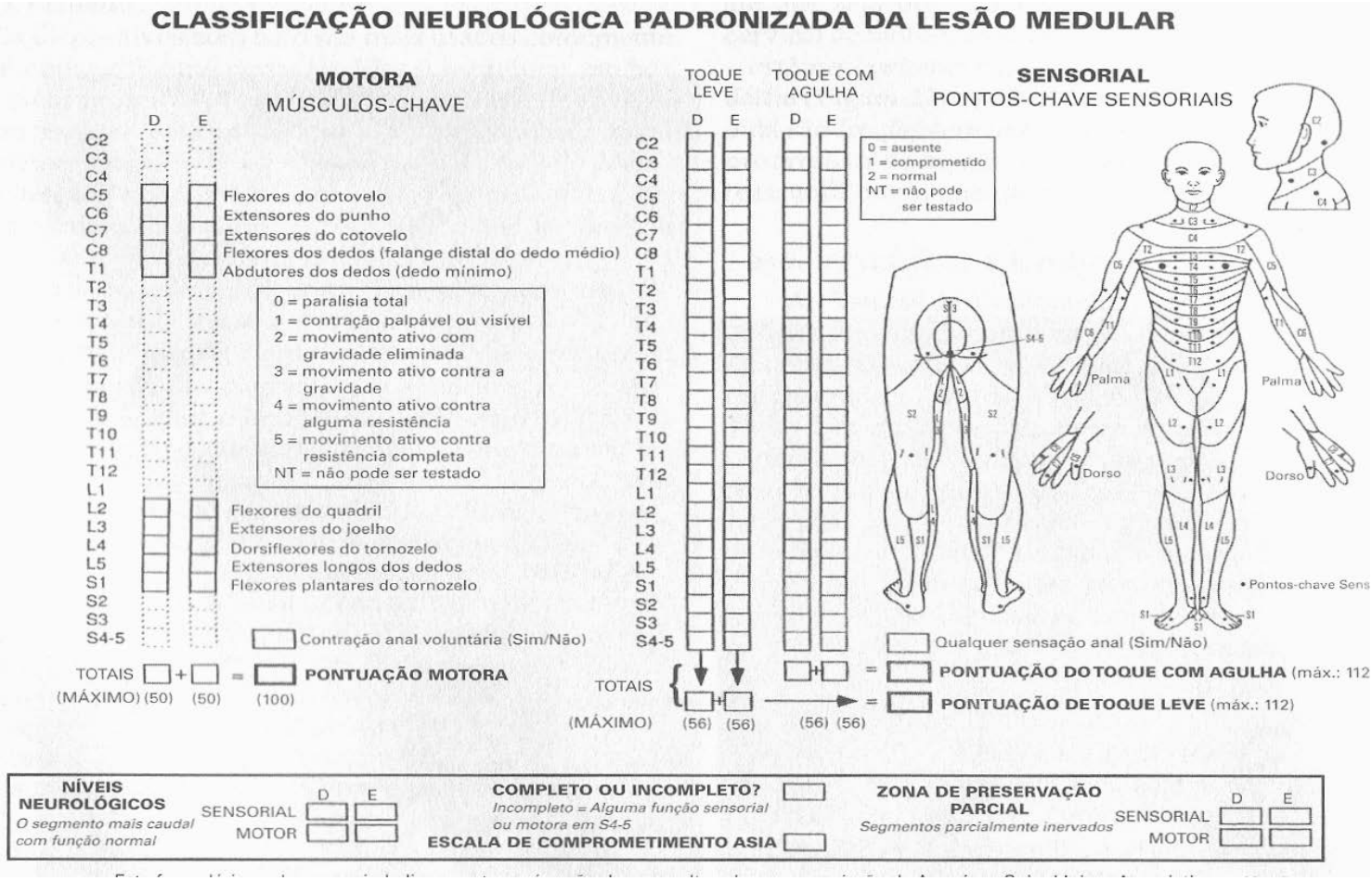


Figura 5: Esquema da Avaliação Neurológica Proposta pela America Spinal Injury Association.

2.6 - Complicações:

As complicações respiratórias são as maiores causas de mortalidade e morbidade em pacientes com TRM. O período mais crítico é durante a internação hospitalar e nos primeiros 6 meses após a lesão. A prevenção e o tratamento inicial das infecções respiratórias como a pneumonia são fundamentais. O comprometimento da força muscular respiratória e da função pulmonar pode limitar, significativamente, a reserva ventilatória necessária para as atividades de vida diária (19, 28).

Outras complicações associadas ao TRM são: dor neuropática, alterações músculo-esqueléticas (osteoporose e ossificação heterotópica), alterações vasculares (trombose venosa profunda, hipotensão postural, disrreflexia autonômica), bexiga neurogênica, intestino neurogênico, úlceras de pressão, espasticidade e automatismos (29).

2.7 - Medidas de Independência Funcional

A independência funcional após o traumatismo raquimedular é uma das maiores expectativas do tratamento. Para uma melhor avaliação e planejamento de intervenções terapêuticas no tangente à reabilitação funcional, a Medida de Independência Funcional (MIF) foi desenvolvida nos EUA na década de 1980 e traduzida para a língua portuguesa por Riberto e colaboradores em 2004 (30, 31) .(32).

A MIF, embora não seja um instrumento de avaliação específico para pacientes com TRM, tem sido bastante utilizada para esta população, permitindo o monitoramento da progressão do paciente no processo de reabilitação e na aquisição de independência para atividades de vida diária (31).

A MIF afere de forma quantitativa o desempenho funcional do indivíduo na realização de atividades que englobam autocuidado, transferências, locomoção, controle esfincteriano e habilidades cognitivas, sendo que para cada tarefa é atribuída uma pontuação que varia de 1 (dependência total) até 7 (independência completa). A pontuação total de MIF varia de 18 a 126, sendo que quanto mais elevada, maior é a capacidade funcional do indivíduo (19, 33).

O TRM leva à incapacidade física, que varia conforme o tipo e grau da lesão, bem como de acordo com o local da estrutura afetada, sendo difícil definir um prognóstico funcional, visto que na fase inicial observam-se diversas manifestações clínicas em decorrência do trauma, tais como choque medular, disrreflexia autonômica e alteração dos parâmetros hemodinâmicos, entre outras.

2.8 – Reabilitação

As perspectivas de reabilitação para pacientes com lesão medular traumática seguem até hoje, na maioria dos centros de reabilitação, um modelo de maximização das funções por mecanismo de compensação dos déficits de controle motor, sensibilidade e equilíbrio, baseado em resultados funcionais esperados de acordo com nível e gravidade da lesão.

As intervenções fisioterapêuticas são consideradas componentes chave do processo de reabilitação para os indivíduos que sofreram lesões traumáticas medulares, pela concepção de recuperar ou alterar as habilidades funcionais e otimizar as atividades sociais (34).

Conforme dados da Rede SARAH de Hospitais de Reabilitação, os pacientes iniciam a melhora de suas funções da primeira semana até o sexto mês, período a partir do qual a chance de melhora espontânea reduz significativamente e instala-se a fase crônica da lesão. Durante todo esse processo, a diminuição de funcionalidade decorrente do trauma impacta não só a vida do indivíduo, mas também da família, daqueles que permeiam seu convívio social e dos sistemas de saúde, uma vez que os gastos com os cuidados diretos podem chegar cerca de 70 mil dólares por ano (35).

As novas perspectivas desenvolvidas nas últimas décadas incitam o fato de que o sistema nervoso central pode sofrer alterações estruturais a partir do aprendizado e de novas conexões neurais por regeneração axonal (36). Tais perspectivas fortalecem o conhecimento sobre neuroplasticidade e enfatizam a necessidade de conhecer a evolução clínica e funcional desses pacientes para que se desenvolvam estratégias e serviços que atendam às reais necessidades dessa população de forma mais efetiva, além de auxiliar na definição do prognóstico ainda nas fases iniciais (37).

A reabilitação física após lesão medular sempre foi contextualizada na premissa de que o sistema nervoso é irreparável e que a melhora funcional está associada à compensação do déficit sensório-motor pelo uso independente da função remanescente e pelo uso de tecnologias assistivas, como dispositivos auxiliares, cadeiras de rodas, pranchas ortostáticas, além do treinamento funcional orientado às tarefas nos autocuidados, em um tratamento que é oneroso e prolongado (29, 38-41). Conforme Ribeiro et al. (2005), o enfretamento das necessidades do cotidiano é um fator decisivo para o desenvolvimento de adaptações espontâneas e aquisição de independência funcional, ainda que sem supervisão profissional. Tais métodos, no entanto, enfatizam a otimização da capacidade funcional máxima após lesão, por mecanismo de adaptação ou compensação, não contemplando a perspectiva de recuperação da função (29, 39, 42).

Os avanços da neurociência têm direcionado os profissionas da área de reabilitação para novas perspectivas na recuperação após lesão medular traumática. Alguns estudos têm hipotetizado a teoria de um modelo de recuperação da função locomotora a partir da plasticidade atividade-dependente. Experimentos em modelos

animais de lesão medular traumática têm suportado as expectativas de que é possível desencadear padrão motor de marcha atividade-dependente. Estudos em humanos demonstram resultados promissores na melhora da marcha em pacientes com lesão medular por meio do uso de suspensão de peso e esteira elétrica (43-45).

O que parece consenso entre os estudos que propõem um novo conceito emergente de reabilitação locomotora após lesão medular traumática é que a recuperação está baseada em prática específica e intensiva e fornecimento de infomação sensorial apropriada (41, 43, 44).

Além dos avanços nas perpectivas de reabilitação sensório-motora por meio da fisioterapia, nas últimas décadas, algumas estratégias de recuperação ou redução de danos têm sido bastante investigadas como potenciais tratamentos para pacientes com lesão medular aguda, embora ainda sem evidências que suportem a recomendação do uso (45, 46).

Dentre as estratégias em investigação, encontram-se:

Resfriamento Local da Medula Espinhal: Em um estudo que avaliou o uso de corticoesteróides por via parenteral e resfriamento local 8 horas após a lesão medular completa de dez pacientes. Foi demonstrada uma taxa melhor do que a esperada de recuperação da função motora e sensitiva, além da redução na taxa de mortalidade em comparação às condutas terapêuticas convencionais (47).

Em um estudo de caso de um jogador de futebol americano com lesão medular completa (ASIA A), Cappuccino e colaboradores descrevem as intervenções terapêuticas utilizadas. A terapêutica instituída incluía cuidados convencionais como descompressão cirúrgica, metilprednisolona e hipotermia sistêmica moderada com objetivo de neuroproteção. Embora os dados na literatura sobre hipotermia terapêutica em lesões medulares sejam escassos, os autores

relatam melhora rápida e significativa nas funções neurológicas, evoluindo para classificação ASIA D. Segundo os próprios autores o desenho do estudo não permite determinar a real contribuição da hipotermia na lesão medular, entretanto sinaliza para uma potencial estratégia terapêutica (48).

Estimulação Elétrica Oscilante: Um campo elétrico negativo tem efeitos tróficos sobre os axônios nas lesões espinhais em vitro e em vivo em animais, com melhora do resultado funcional. A estimulação baseia-se em um campo estimulador oscilante desenvolvido para pesquisa em humanos e aprovado pelo FDA (Food and Drug Administration) para um a pesquisa fase 1. Foram incluídos 10 pacientes com lesão medular completa entre C5 e T10 e sem transecção, avaliada na ressonância magnética. Todos os participantes receberam o protocolo National Acute Spinal Injury Study com metilprednisolona. Após o tratamento para estabilização, todos pacientes inclusos no estudo mantiveram-se sem potenciais evocados somatossensitivos (PESS) abaixo do nível da lesão após a cirurgia ou por 48 horas, sendo então submetidos ao implante da estimulação elétrica de campo oscilante dentro de 18 dias. Os pacientes foram submetidos à avaliação a cada 2 semanas após a implantação, esta retirada em 15 semanas. A função neurológica foi avaliada com base na pontuação ASIA, escala visual analógica para dor e potencial evocado somatossensitivo em 6 semanas, 6 meses e 1 ano. Não houve complicações na inserção da estimulação elétrica oscilante. A sensibilidade tátil aumentou em média 25,5 pontos e a dolorosa, 20,4. O escore motor aumentou 6,3 pontos com significância estatística. Os autores concluíram que o uso da estimulação elétrica oscilante é seguro, confiável e de fácil aplicação, entretanto, tais resultados não suportam ainda uma recomendação (49).

Macrófagos Autólogos: Um estudo fase 1, aberto, não randomizado, avaliou a segurança e tolerabilidade de macrófagos autólogos incubados administrados a pacientes com lesão medular completa aguda. A terapia foi testada inicialmente em modelos animais com transecção e contusão da medula espinhal, demonstrando a recuperação da função motora. O processo desenvolvido para uso clínico consistiu em isolar os monócitos a partir do sangue do doente e incubá- los com derme autóloga. Os macrófagos autólogos incubados resultantes foram injetados em medula espinhal de 8 pacientes com classificação ASIA A, imediatamente abaixo do nível da lesão, no prazo de 14 dias. Os pacientes foram avaliados através da escala ASIA, monitoramento eletrofisiológico (evocado motor e/ ou potenciais evocados somatossensitivos) e ressonância magnética. Dos oito pacientes incluídos no estudo, três apresentaram recuperação da função neurológica motora e sensitiva significativa (ASIA C). Durante o período de estudo, eventos adversos graves foram encontrados, sendo dois casos de embolia pulmonar e um caso de osteomielite. Segundo os autores, estes eventos parecem ser semelhantes aos encontrados em outros pacientes lesados medulares e não são considerados como conseqüência da terapia experimental (50).

Agentes Neuroprotetores: Estudos pré-clínicos têm atribuído propriedades neuroprotetoras para o antibiótico minociclina. Estudos em animais e ensaios clínicos iniciais apoiam a sua utilização em várias doenças neurológicas. Em modelos animais de lesão medular, a minociclina melhorou os resultados neurológicos e histológicos, promoveu redução neuronal e apoptose oligodendroglial, diminuição da ativação da microglia e da inflamação. Um único estudo, humano, duplo-cego, randomizado, controlado por placebo de administração de minociclina após a lesão da medula espinhal foi realizado para fins de otimização

de dose, avaliação de segurança e para estimar mudanças de desfechos. Resultados neurológicos e funcionais e eventos adversos foram comparados entre os indivíduos que receberam 7 dias de minociclina intravenosa (n = 27) ou placebo (n = 25), após lesão medular traumática aguda. O desfecho secundário utilizado para avaliar as diferenças neurológicas entre grupos que podem justificar uma investigação mais aprofundada foi a recuperação motora em um 1 ano, usando a escala ASIA. Elevação transitória das enzimas hepáticas em um paciente foi o único evento adverso provavelmente relacionado com a droga em estudo. Pacientes que receberam minociclina apresentaram aumento de seis na avaliação motora quando comparados com os pacientes que receberam placebo, sem significância estatística. Os autores concluem que embora os resultados obtidos não demonstrem significância estatística, o uso de minociclina mostrou-se seguro, merecendo uma investigação mais aprofundada em ensaio multicêntrico de fase III (51).

Tratamento com Celulas Tronco: O tratamento com células tronco após lesão da medula espinhal tem sido considerado uma estratégia terêutica como forma de reparação da lesão (52, 53). O cordão umbilical é uma fonte de células tronco da medula devido à seus componentes hematopoiéticos e mesenquimais. O emprego de células tronco presentes no cordão umbilical humano tem sido utilizado para o tratamento de desordens do sangue, assim como em experimentos regenerativos e para o tratamento de outras doenças neurológicas (54, 55). Estas células são particularmente interessantes para o transplante em virtude de serem fáceis de obter, manter e expandir em laboratórios com condições obviamente apropriadas.

2.9 – Biomarcadores na Lesão Medular:

Importantes progressos inegavelmente ocorreram ao longo dos últimos 30 anos nas condições médicas, cirúrgicas e na reabilitação de pacientes com lesões agudas e crônicas medulares (56, 57, 58). Entretanto, apesar das inúmeras pesquisas, não há tratamento eficaz e convincente que substancialmente melhore a função dos pacientes com TRM.

O emprego dos biomarcadores tem sido objeto de estudo em várias doenças neurológicas onde o início incipiente é frequentemente mensurado em meses e o diagnóstico pode ficar incerto por anos. Todavia, a natureza aguda do traumatismo raquimedular não deixa dúvidas sobre o momento do trauma e o início das manifestações neurológicas. Desta forma a utilização de biomarcadores pode ser útil na determinação da evolução das lesões primárias e na procura por um novo ou tratamento neuroprotetor mais efetivo.

Assim como outras alterações neurológicas, o desenvolvimento de tratamentos em um cenário pré-clínico laboratorial, assim como uma avaliação e acompanhamento de uma evolução clínica, são elementos importantes no desenvolvimento de novos tratamentos para o lesionado medular.

Uma nova abordagem para avaliação com comprometimento medular na fase aguda é mensuração de biomarcadores no líquido cefalorraquidiano. O TRM ocasiona uma necrose neuronal, seguida de uma degeneração do axônio, com apoptose, morte ou necrose de nervos em dias ou semanas. O líquido cefalorraquidiano circula a medula espinhal e é capaz de perceber alterações de proteínas e metabólitos do tecido nervoso (59).

Atualmente poucos estudos foram realizados com avaliação de marcadores no sangue ou no líquido cefalorraquidiano de pacientes com lesão medular. A Tabela 3 resume as principais características destes estudos. Na avaliação destes estudos as proteínas S-100β e neurônio específica enolase foram as mais estudadas (60-71).

Tabela 3. Estudos com Biomarcadores no Trauma Raquimedular:

Estudo	Biomarcador	Liquido Cefalorraquidiano/ Sangue	Resultado Mais Importante
Van Dongen	S-100β	Ambos	Sem alterações
Van Dongen	S-100β	LCR	Elevação
Brisby	S-100β, NSE	LCR	Elevação NFL e S-100β
Kunihara	S-100β	Ambos	Elevação S-100β
Ohta	MBP	Ambos	Sem alterações
Guez	GFAP, NFL	LCR	Sem alterações
Shiiya	S-100β, tau	LCR	Elevação S-100β
Marquardt	S-100β	Sangue	Elevação = Piora Desfecho
Marquardt	S-100β	Sangue	Elevação = Piora Desfecho
Brunnekreef	S-100β	LCR	Sem alterações
Winnerkvist	S-100β, GFAP, NFL	LCR	Elevação todos
Khaladj	S-100β	Ambos	Elavação S-100β

Abreviaturas: LCR = liquido cefalorraquidiano, GFAP = Glial Fibrilary acidic protein, MBP = Myelin Basic Protein, NFL = Neurofilament Protein, NSE = neuron-specific enolase.

Esta tese tem como objetivo direcionar a avaliação de três biomarcadores que podem ser avaliados no sangue de pacientes com TRM: a Enolase Neurônio-Específica, Fator Neurotrófico derivado da Linhagem de Celulas Gliais e a Interleucina 6.

2.9.1. Enolase Neurônio-Específica (NSE - Neuron Especific Enolase): é uma enzima glicolítica (2-fosfo-D-glicerato hidrolase) que existe na forma de diversas isoenzimas diméricas: alfa-alfa, alfa-beta, beta-beta e gama-gama. As isoenzimas gg e ag são também conhecidas como enolases neurônio-específica (NSE) que são encontradas principalmente nos neurônios e nas células neuroendócrinas (72-74). A NSE é o único marcador que avalia diretamente dano funcional aos neurônios. Ela é liberada passivamente por destruição celular (28) e suas concentrações aumentadas, após o dano neural, podem ser mensuradas em sangue periférico ou líquor (75, 76). A especificidade da NSE é alta e a variabilidade relacionada a sexo e idade é baixa(77). Um dos principais problemas associados com seu uso como marcador de dano cerebral é a hemólise. Os eritrócitos contêm grande quantidade de NSE e a hemólise pode, portanto, causar um marcado aumento de NSE no sangue (75).

Concentrações elevadas de NSE são detectadas em pacientes com carcinoma medular de tireóide, tumores de células da ilhota pancreática, feocromocitoma, neuroblastoma e carcinoma de pequenas células de pulmão, sendo um marcador diagnóstico de relativa especificidade (85%), possivelmente em função de serem tumores neuroendócrinos. Pode ser usado para monitorar os efeitos da terapia e indicar recidivas antes das evidências clínicas.

Estudos experimentais têm demonstrado que a elevação da NSE após lesões cerebrais corticais (78). A NSE foi efetiva em predizer os desfechos neurológicos e

de sobrevida após paradas cardiorrespiratórias (79). Também há uma elevação da NSE em pacientes com epilepsia do lobo temporal (80, 81).

Brisby et al., comparou o comportamento da NSE em 15 pacientes submetidos a cirurgia de hérnia de disco lombar com um grupo controle. Não houve diferenças entre a NSE nos dois grupos (60).

2.9.2. Fator Neurotrófico derivado da Linhagem de Celulas Gliais - *Glial Cell Line-derived Neurotrophic Factor* (GDNF):

É um fator neurotrófico altamente conservador. A forma recombinante desta proteína promove a sobrevivência e diferenciação de neurônios dopaminérgicos em cultura, e foi capaz de prevenir apoptose de neurônios motores induzida por axotomia. Apresenta propriedades regenerativas nas células cerebrais e neurônios moteres em modelos animais (82).

Não há estudos avaliando o comportamento da GDNF em pacientes com TRM.

2.9.3. Citoquinas Neuroinflamatórias:

As neurocitoquinas neuroinflamatórias, como as interleucinas 6 (IL-6) e 8 (IL-8), Fator de Necrose Tumoral α - Tumor Necrosis Factor-α (TNF- α) foram estudadas no Acidente Vascular Cerebral (AVC) e no Traumatismo Cranio-Encefálico (TCE) como biomarcardores em potencial.(83). As citoquinas pertencem a um grupo de pequenas glicoproteínas que são produzidas em resposta a um antígeno e foram originalmente descritas como mediadores que regulam o sistema imune adaptativo.

As citoquinas estão superestimuladas no sistema nervoso central em várias doenças, como no AVC, Esclerose Múltipla e Neurotrauma. As citoquinas estão

expressas não somente nas células do sistema imune (micróglia e plasma), mas também nas células residentes no cérebro incluindo neurônios e glia (84).

Níveis elevados de citoquinas no liquido cefalorraquidiano foram descritos em modelos animais e correlacionou-se com um aumento da cascata inflamatória secundária a lesão medular. A IL-6 aumentou significativamente nas primeiras horas tanto em modelos animais quanto em humanos (85) (86).

A Interleucina-6 (*IL-6*) é uma proteína que em humanos é codificada pelo gene *IL6* . Age como uma citocina pro-inflamatória e anti-inflamatórios (87). É secretada por células t e macrófagos para estimular a resposta imune ao trauma, especialmente queimaduras ou outro dano ao tecido levando a inflamação. A IL-6 é também uma citocina produzida a partir de músculo e é elevada em resposta a contração muscular. Ela é significativamente elevada com exercício e precede o aparecimento de outras citocinas na circulação. O Papel da IL-6 como uma anti-inflamatório citocina é mediada por meio de seus efeitos inibidores TNF-alfa e IL-1 e ativação de IL-1ra e IL-10 (88).

Mais recentemente Kwon et. avaliou as concentrações de IL-6 e IL-8 no líquido cefalorraquidiano de 27 pacientes com trauma raquimedular e comparou com a severidade do copromentimento. Neste estudo estes dois marcadores não correlacionaram-se com a gravidade do mesmo (89).

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4 – Objetivos

3.1 - Objetivos

3.1.1. Relacionados no Artigo 1

Descrever as Causas das Lesões Medulares de um hospital especializado em trauma na cidade de Porto Alegre e comparar com outros centros no Brasil.

Avaliar as taxas de mortalidade, tempo de ventilação mecânica, tempo de internação destes pacientes.

Comparar o panorama brasileiro de TSCI com o de outros países.

3.1.2. Relacionados no Artigo 2

Avaliar a Recuperação Funcional em pacientes com Trauma Raquimedular provocado por lesões de arma de fogo mediante o emprego da Escala de Medida de Independência Funcional.

Avaliar e Funcionalidade mediante o emprego da MIF no momento da alta e 6 meses após a lesão medular por arma de fogo.

Classificar mediante o emprego do escore ASIA os pacientes com lesão medular por arma de fogo no momento da alta e 6 meses após.

3.1.3. Relacionados no Artigo 3

Avaliar os Niveis Séricos dos Biomarcadores: Neuronio Específico Enolase, Irterleucina-6, e Fator Neurotrófico Derivado das Celulas Gliais em pacientes com Trauma Raquimedular Isolado.

Avaliar o comportamento destes Biomarcadores nas primeiras 48 horas e comparar com o grupo controle, correlacionando as alterações clínicas e o prognóstico nos pacientes com TRM.

5 – Artigos em Inglês

FIREARM LESIONS: A MAJOR CAUSE OF TRAUMATIC SPINAL CORD INJURY IN BRAZIL

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ABSTRACT

Introduction: The world epidemiology of the traumatic spinal cord injury (TSCI) is not completely established. Given the long life expectancies currently enjoyed by persons with SCI as well as trends toward increasing age at time of injury, there has been increased speculation and concern about the ability of our health care system to deal effectively with the potential needs of an aging SCI population

Objectives: Here we examine the causes and injury characteristics of TCSI patients who have been treated in a Brazilian reference trauma center and review the Brazilian reality of TCSI. Compare our data with other countries.

Material and Methods: Prospective cohort study conducted in the Intensive Care Unit (ICU) of a large public Brazilian hospital. All patients with acute TCSI who were admitted in our center from 2010 to 2013 were included in the study.

Results: The group was composed of 94 patients, mean age (±S.D.) of 34.5 (±14.06) years, being 88 (90.4%) males. Forty seven patients (50.0%) had cervical injuries, thirty five (37.2%) have thoracic injuries and twelve (12.8%) had lumbar trauma. The major cause of TCSI in our cohort was firearm lesions, observed in 34 (36.2%) patients. Our observation is in line with medical literature, showing that firearms are a major cause of TSCI in Brazil.

Conclusions: Lesions provoked by firearms are an important cause of TSCI causes in Brazil, a country that share TSCI causal similarities with Sub-Saharan, North Africa, Middle East and other Latin America regions. Reducing violence is an important step in preventing TSCI in these regions.

Keywords: firearms, traumatic spinal cord injury**,** epidemiology

Introduction

Spinal cord injury (SCI) is defined as any lesion of the spinal cord that causes neurological damage. Spinal cord injury (SCI) occurs in 15 to 40 new patients/million/year (1, 2). The causes of these injuries range from motor vehicle accidents and community violence to recreational activities and workplace-related injuries (3). Survival has improved along with a greater appreciation of patterns of presentation, complications and long-term prognosis (4).

Patients with SCI involuntarily place a heavy burden on the health care system, not only in the phase of acute care, but also in the first years following injury (5). Some of the additional problems resulting from patients with SCI include secondary complications needing hospitalization (eg urinary tract infection and pressure sores), the need for home care services and for extra physician contacts and other health care problems (5). SCI-related problems in the U.S. cost approximately US $9.7 million per year (6).

In recent years, the number of traumatic causes of spinal cord injury (TSCI) is increasing. Since there is no cure for TSCI, recognition of its causes can lead to prevention and control programs. Epidemiological studies in the U.S. reveal an incidence of 30/40 cases per million of the population each year, with a prevalence of 72-250.000 cases of TSCI (ref). Typical patients are males, between 15 and 34 years old, victims of traffic accidents and paraplegic. Little is known about spinal cord injury in developing countries.

In this article, we examine causes and some clinical aspects of patients with TSCI in our hospital, a typical large metropolitan Brazilian public hospital, and compare our results with other studies in Brazil. Moreover, we analyze the differences between the Brazilian scenario and other world regions regarding

TSCI. Delineating causes is of paramount importance to prevent TSCI. We hope our study help to sensitize public opinion for a sad reality occurring in Brazil.

Methods.

Patient population

This was a prospective cohort study conducted in the Intensive Care Unit (ICU) of Cristo Redentor Hospital, in Porto Alegre, Brazil, from March 2010 to march 2013. .Porto Alegre is the capital of the state of Rio Grande do Sul in southern Brazil. The city has a population of 1,416,735 distributed in an area of 496.8 km2. Porto Alegre is the capital of Rio Grande do Sul state. It's the fourth highest Human Development Index (HDI) in the country (7). In Brazil, one of the largest public health systems in the world, the Unified Health System (SUS) has an agreement with almost all the hospitals. (8). In this network are public and private university hospitals, which guarantee to all citizens the constitutional right of access to health care.

Known as the Emergency Zone North Hospital, Cristo Redentor is reference in serving accident victims, being the largest in the south of Brazil. Cristo Redentor Hospital is a 290-bed trauma care and neurosurgery regional referral center, and overall approximately 300 patients are referred to the hospital per day. The ICU functions as a closed unit, with 29 beds and care provided by physicians in routine practice and on duty, and physiotherapists during the day shift. The overall mortality rate in the hospital is 20%.

All patients (≥ 24 hours), (aged ≥ 18 years), with isolated TSCI admitted to the ICU during the period of 2010-2013 were included in this study. Exclusion criteria were head trauma or other traumas not directly associated with the spinal

injury. Figure 1 shows the schematic diagram of patient selection. The study was approved by the Research Ethics Committee of the institution, (#11-013), and was conducted in accordance with the provisions of the Declaration of Helsinki. Informed consent was obtained from all participants' guardians or caregivers.

The demographic and epidemiological information regarding the admission and treatment approaches and records of the Group Hospital readmissions were collected from electronic medical records. Neurological and functional assessments were performed during hospitalization at discharge. Neurological Classification of Spinal Cord Injury (ASIA), through sensory and motor examination, evaluates the tactile and painful in 28 dermatomes, ranking among normal (2), decreased (1) and absence of sensory response (0). The motor examination assesses muscle strength graded from zero (no muscle contraction) to five (high force against manual resistance) in 10 specific myotomes, divided into upper and lower limbs bilaterally. The Asia scale also incorporates the Frankel scale, consisting of five levels: sensory and motor function complete (A); complete sensory and motor deficit incomplete (B), sensory and motor function incomplete nonfunctional (C); incomplete sensory and motor function functional (D) and standard motor and sensory function (E) (9)

Insert Figure 1 about here

Statistical analysis

Continuous variables were expressed as mean (± standard deviation) and categorical variables as count and percentage. Comparisons between groups were performed using the Student *t* test or one-way ANOVA for continuous variables and the chi-square test for categorical variables. Data were analyzed using the Statistical Package for the Social Sciences, version 18.0 (SPSS, Chicago, IL), with the level of significance set at $p < 0.05$.

Spinal Cord Trauma Brazilian Literature

In a PUBMED survey including Brazil AND (arm fire OR gun OR gunshot OR guns OR firearm OR shooting) AND (spine OR spinal) AND (lesion OR injury OR trauma) we were able to recover 16 articles. From these, 5 were excluded for being case/report study. We review the remaing articles with attention to the causes of TCSI. (10-20)

RESULTS

Clinical Features of the Patients

Clinical and demographic data of the patients are presented in Table 1 and Table 2. The group was composed of 94 individuals, with mean (±S.D.) age of 34.5 (±14.06) years, being 88 (90.4%) males. Forty seven patients (50.0%) had cervical injuries, thirty five (37.2%) have thoracic injuries and twelve (12.8%) had lumbar trauma.

The major cause of TCSI in our cohort was firearm lesions, observed in

34 (35%) patients. These patients were younger. Firearm related TSCI is a common cause of spinal trauma in Brazil (Table 3). Cervical TSCI was mostly observed after falls, the lesion also associated with lower ASIA scores and the highest mortality. Thoracic lesions were more commonly related to vehicle accidents, while lumbar lesions were more commonly associated with firearm lesions. Complete, Frankel A lesions occurred in 49 (52.12%) patients.

Forty eight patients (51.06%) underwent to surgical treatment but from these, only seven had trauma related to firearms.

Insert Table 1 about here

Insert Table 2 about here

Insert Table 3 about here

Discussion

The incidence of spinal cord injury in Brazil is not well established. However, according to official governmental data, trauma is the leading cause of spinal cord pathology in Brazil (80% of all medullary lesions), with an incidence of 40/million/year (21). From these patients, 80% are men and 60% are between 10 and 30 years old (4, 22). The causes of TSCI in Brazil are also not well documented, but according to recent governmental statistics (2013) the two leading causes of TSCI in Brazil are first, vehicle accidents (with progressive lowering incidence) and second, spinal cord lesions provoked by firearms (23). Vafa Rahimi-Movaghar et al. reviewed the incidence of TSCI in developing countries and found 8 studies showing an incidence of TSCI in Brazil with an incidence ranging from 10 to 71 cases per million inhabitants (1, 24).

In Table 3 we summarize the major works on the etiology of traumatic spinal cord injury in Brazil (14, 17, 19, 20, 25-28).

The epidemiology of traumatic spinal cord injury is better known in the U.S., Western European countries, Australia and some parts of Asia, like Japan and South Korea. However, in a large part of the world, statistical data is still lacking. In an attempt to examine existing literature, Cripps RA et al. mapped the TSCI epidemiology worldwide (29). These authors observed that four-wheeled motor accidents were the major cause of TSCI in North America, Western Europe and Australia. In South-east Asia, two-wheeled (and non-standard) road transport was more common. In Southern Asia and Oceania, falls from heights were the primary causes of TSCI. On the other hand, violence, usually firearm-related TSCI is higher in North America (15%) when compared to Western Europe (6%) or Australia (2%). The highest rates of firearm-related TSCI are in Sub-Saharan (35%), north Africa

(24%), Middle East (24%) and Latin America (22%). Violence-related TSCI have been frequent in zones of conflict, like Afghanistan (30).

When compared to similar studies from several other countries, our results show a disproportionately high incidence of violent injuries, particularly gunshot wounds in a typical metropolitan Brazilian hospital. Revising literature, we conclude that traumatic spinal cord injuries have been poorly reported in Brazil. When it is reported, most authors appoint to high rates of firearm-related TSCI in our country. When compared with rest of the world, TSCI causes in Brazil share similarities with Sub-Saharan countries, North Africa, Middle East and other countries in Latin America. Brazil is among the 20 more violent countries in the world and this sad aspect might be reflecting in the epidemiology of spinal cord injuries. Reducing violence in Brazil can help prevent new traumatic spinal cord injuries caused by gunshot wounds.

Conflict of interest

None declared.

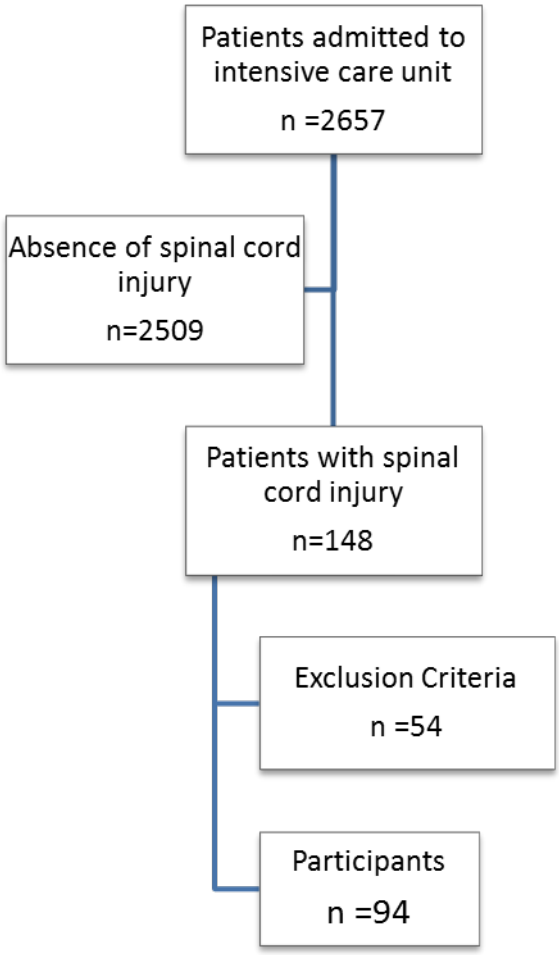

Figure 1: Flow diagram for total patients included in the study.

Table 1. Characteristics of Patients

Variables	**Total n = 94**
Age (years)[a]	34.5 ±14.1
Days in hospital[b]	39.3±28
Days in MV	
Male sex – n (%)	88 (93.6%)
Survivals	81 (86.2%)
Cause	
Firearm	34 (36.2%)
Fall	22 (23.5%)
Motorcycle Accident	13 (13.8%)
Car Accident	16 (17.0%)
Swimming	09 (09. 6%)
Spine Level	
Cervical	47 (50 %)
Thorax	35 (37.2%)
Lumbar	12 (12.8%)

[a] Values are expressed as mean ± standard deviation.

[b] Values are expressed as mean ± median.

MV = mechanical ventilation

Table 2. Variables According with Cause of Spinal Cord Injury

Variables	Cause of TSCI			*p*
	Weapon	**Fall**	**Car**	
	n=35 (37,2%)	**n=30 (31.9%)**	**n=29 (30.9%)**	
Age (years)[a]	29.2±12.5	39.2±16.4	36.0±11.4	**0.012**[b]
Days in hospital[a]	43.7±36.6	35.4±29.7	37.8±30.2	0.567[b]
Days in MV[a]	11.7±16.4	10.6±15.9	06.7±14.8	0.435[b]
MV	22 (62.9%)	15 (50.0%)	12 (41.4%)	0.222[c]
Male sex – n (%)	33 (94.3%)	29 (96.7%)	26 (89.7%)	0.534[c]
Survivals	31 (88.6%)	22 (73.3%)	28 (96.6%)	**0.031**[c]
Spine Level				
Cervical	13 (37.1%)	22 (73.3%)	12(41.4%)	
Thorax	11 (31.4%)	07 (23.3%)	17 (58.6%)	
Lumbar	11 (31.4%)	01 (03.3%)	00 (00.0%)	**< 0.0001**[c]
Surgery	07 (20.0%)	20 (66.7%)	21 (72.4%)	**< 0.0001**[c]
Frankel A	21 (60.0%)	15 (50.0%)	13 (44.8%)	0.462[c]
Asia Motor Upper Limb	38.8±16.5	20.6±18.7	37.6±18.3	**<0.0001**[b]
Asia Motor Low Limb	03.5±10.5	03.3±09.8	05.5±13.1	0.699[b]
Asia Tactile	55.6±28.1	36.1±31.3	59.4±29.8	**0.006** [b]
Asia Pain	55.6±28.1	36.0±31.2	59.9±29.2	**0.005**[b]

TSCI = Traumatic Spinal Cord Injury; MV = Mechanical Ventilation;

[a] Values are expressed as mean ± standard deviation.

[b] One way ANOVA.

[c] Pearson's chi-square test.

Significant if $p<0.05$

Table 3. Causes of Brazilian TSCI

Author	Year of Study	Number of Patients	Fire Arm Lesions Patients %	Major Cause %
de Amoreira	2012	93	11.8	MVA
De Biase	2011	20	1	MVA (50.0)
Vall	2011	109	49	Fire Arms
Costacurta	2010	106	42.6	Fire Arms (42.6)
Blanes	2009	60	63.3	Fire Arms (63.3)
Vall	2006	32	71.8	Fire Arm
Rogano	2003	81	NI	NI
Sacomani	2003	71	43.7	Fire Arms (43.7)
Flores	1999	45	45	Fire Arms (100)
Da Paz	1992	108	27.8	MVA (41.7)
Barros Filho	1990	428	36.7	Fire Arm (36,8)

MVA=Motor Vehicle Accident, NI = Not Informed

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Functional Rehabilitation of Acute Firearm Spinal Cord Injuries: A Prospective Cohort Study

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ABSTRACT

Introduction: Studies examine functional rehabilitation after firearm traumatic spinal cord injury (TSCI) are lacking in literature. Here we report results of a study evaluating functional recovery after traumatic spinal cord injury.

Material and Methods: Prospective cohort study conducted in patients with severe TSCI with the objective of evaluates functional recovery after firearm traumatic spinal cord injury (TSCI). All survivals patients of isolated acute TCSI who were attended in our center from 2010 to 2013 were included in this study. Patients were divided in two groups if TSCI, those with lesions provoked by firearms was provoked by firearm or other causes. During hospitalization all patients were submitted to intensive rehabilitation and followed in a rehabilitation program after discharge. They were evaluated with ASIA and FIM at the time of the hospital discharge and six mounts latter.

Results: The cohort was composed by 81 patients, mean age (±S.D.) of 32.6 (±12.2) years, being 76 (93.8%) males. Patients with TSCI caused by firearms showed lower degree of impairment than other patients in ASIA motor superior, because a larger number of patients in the group of firearm lesions showed lumbar woods. However, in the other scales we did not observed this difference. After six months, patients showed significant improvement in ASIA and FIM scales. The degree of improvement was similar between patients with TSCI caused by firearms or others.

Conclusions: TSCI provoked by firearms are an important cause of spinal lesion and neurological deficits in Brazil. Functional recovery in severe TSCI provoked by firearms is limited but similar than severe TSCI provoked by falls or a
accidents.

Key words: Functional Recovery, Physiotherapy, Acute Firearm Spinal Cord Injuries.

Introduction

Spinal cord injury (SCI) is defined as any lesion of the spinal cord that causes neurological damage. Trauma is a major and increasing cause of SCI. Epidemiological studies in the U.S. reveal an incidence of 30/40 cases per million of the population each year, with a prevalence of 72-250.000 cases of TSCI (1). Typical patients are males, between 15 and 34 years old, victims of traffic accidents and paraplegic. Little is known about spinal cord injury in developing countries. The causes of these injuries range from motor vehicle accidents and community violence to recreational activities and workplace-related injuries (1). Survival has improved along with a greater appreciation of patterns of presentation, complications and long-term prognosis (2).

Patients with SCI involuntarily place a heavy burden on the health care system, not only in the phase of acute care, but also in the first years following injury (3). Some of the additional problems resulting from patients with SCI include secondary complications needing hospitalization (e.g. urinary tract infection and pressure sores), the need for home care services and for extra physician contacts and other health care problems (3-4). SCI-related problems in the U.S. cost approximately US $9.7 million per year (4).

One of main causes of TSCI in countries in development or in zones of conflict is TSCI provoked by firearms. In spite of being common in these regions, rehabilitation of patients with TCSI provoked by gunshots have been poorly investigated. In this article, we report results of a prospective cohort study designed to evaluate rehabilitation in TSCI caused by firearms. We hope our results might help to plan better treatment or rehabilitation program for those patients with TSCI due to firearms.

The magnitude and rate of recovery depends on the initial injury severity. Physical therapy (PT) is an integral component of all spinal cord injury (SCI) rehabilitation programs and includes a variety of interventions that address in body function, structure, activity limitation and participation. Body function refers to impairments in sensation or motor function, range of motion (ROM) limitations and musculoskeletal pain (5, 6). Participation refers to activities that contribute to social and leisure skill roles, such as homemaker, sports participant, or college student.

The rehabilitation process typically includes multiple phases that take place over a period of weeks, months, or years. For many patients with SCI, the primary goals include maximizing independence with basic skills (bed mobility, wheelchair management, and transfers), progression to ambulation if appropriate, caregiver training, provision of equipment, and education (on topics such as pressure relief or medical complications).

A number of investigations have examined the impact of the timing, intensity, or duration of inpatient rehabilitation programs on rehabilitation outcomes, and have associated participation in inpatient rehabilitation for SCI with functional gains (7-10).

The Guide to Physical Therapist Practice published by the American Physical Therapy Association describes preferred practice patterns to provide clinical guidelines. (11). The rate of recovery is measured by the relative change in the motor and sensory scores over time.

The objective of this study is to evaluate functional recovery after traumatic spinal cord injury in a trauma scenario.

Methods.

Patient population

This was a prospective cohort study conducted in the Intensive Care Unit (ICU) of Cristo Redentor Hospital, in Porto Alegre, Brazil, from March 2010 to march 2013. Porto Alegre is the capital of the state of Rio Grande does Sul in southern Brazil. The city has a population of 1,416,735 distributed in an area of 496.8 km2. Porto Alegre is the capital of Rio Grande do Sul state. It's the fourth highest Human Development Index (HDI) in the country (12). In Brazil, one of the largest public health systems in the world, the Unified Health System (SUS) has an agreement with almost all the hospitals (13). In this network are public and private university hospitals, which guarantee to all citizens the constitutional right of access to health care.

Known as the Emergency Zone North Hospital, Cristo Redentor is reference in serving accident victims, being the largest in the south of Brazil. Cristo Redentor Hospital is a 290-bed trauma care and neurosurgery regional referral center, and overall approximately 300 patients are referred to the hospital per day. The ICU functions as a closed unit, with 29 beds and care provided by physicians in routine practice and on duty, and physiotherapists during the day shift. The overall mortality rate in the hospital is 20%.

All patients (≥ 24 hours), (aged ≥ 18 years), with isolated TSCI admitted to the ICU during the period of 2010-2013 were included in this study. Exclusion criteria were head trauma or other traumas not directly associated with the spinal injury. Figure 1 shows the schematic diagram of patient selection. The study was approved by the Research Ethics Committee of the institution, (#11-013), and was

conducted in accordance with the provisions of the Declaration of Helsinki. Informed consent was obtained from all participants' guardians or caregivers.

The demographic and epidemiological information regarding the admission and treatment approaches and records of the Group Hospital readmissions were collected from electronic medical records. Neurological and functional assessments were performed during hospitalization and 6 months after.

Neurological Classification of Spinal Cord Injury (ASIA), through sensory and motor examination, evaluates the tactile and painful in 28 dermatomes, ranking among normal (2), decreased (1) and absence of sensory response (0). The motor examination assesses muscle strength graded from zero (no muscle contraction) to five (high force against manual resistance) in 10 specific myotomes, divided into upper and lower limbs bilaterally. The Asia scale also incorporates the Frankel scale, consisting of five levels: sensory and motor function complete (A); complete sensory and motor deficit incomplete (B), sensory and motor function incomplete nonfunctional (C); incomplete sensory and motor function functional (D) and standard motor and sensory function (E) (14)

Functional capacity was measured by means of the Functional Independence Measure (FIM), validated for the Brazilian population, which measures quantitatively the functional performance of the individual in carrying out activities that include self-care, transfers, locomotion, sphincter control and cognitive abilities. For each task is assigned a score ranging from 1 (total dependence) to 7 (complete independence). The total score FIM ranges from 18 to 126, whereas the higher, the greater the functional capacity of the individual.

Physiotherapy Program:

During the period of hospitalization the patient received 2 sessions daily physiotherapy. After discharge, the patient was referred to the Rehabilitation Service which consisted of physical, occupational and speech therapy, psychologist and also medical assistance. Outpatient program included a minimum of 6 weeks, 3 times a week.

The Physiotherapy Activities during the hospital were: airway and respiratory management (non-invasive ventilation, deep breathing exercises, bronchial hygiene) musculoskeletal treatment modalities (body positioning, range of motion/stretching exercises, endurance exercises), skin management, mobility training (bed mobility, wheelchair mobility, gait, transfers), strengthening exercises, upright work. After discharge the patient was referred to the Rehabilitation Service which was added equipment evaluation and educations as well as they were invited to participated in interdisciplinary conferences.

Insert Figure 1 about here

Statistical analysis

Continuous variables were analyzed by the Student t-test with Levens's test, and reported as mean and standard deviation (±S.D.). Categorical variables were analyzed by the Chi-square test and are expressed as odds ratio and 95% confidence interval (O.R.; 95%CI). The effect of physiotherapy was evaluated using a general linear repeated measure ANOVA with ASIA scores or FIM scores evaluated during hospitalization or six months latter as between-within subject

factors and the cause of the lesion (firearm lesions or other causes) used as independent between-group variable (22). The level of significance in the multivariate test was established using Wilk's Lambda test. Thus, in the present study each patient was evaluated at two different times (a repeated measures approach), and the two groups of patients were split according to cause of TSCI (firearm lesions or other causes). For the ASIA or FIM scores, the results are reported as mean (±SD) and the level of significance for differences among the two different evaluations (during acute event and six months latters), the differences between the two groups of cause of the spinal lesion, and the interaction of physiotherapy and the cause of the lesion in order to assess if these two groups of patients responded differently to rehabilitation. The results of these analyses were plotted on SPSS generated graphs in order to facilitate the understanding of the analysis model used and the variability of the rehabilitation in the two groups of patients studied. All statistical analyses were performed using the SPSS version 20 software (IBM Corp., 2011, USA). In all analyses, a significant difference was considered at $p<0.05$.

RESULTS

Clinical and demographic data of the patients are presented in Table 1. Eighty one individuals were followed in this cohort study. Mean (±S.D.) age was 32.6 (±12.2) years old. Seventy six patients (93.8%) were males. Patients with gunfire related TSCI were younger, with mean age of 27.3 (±10.4) years-old when compared with patients with TSCI associated with other causes that had mean age of 35.9 (±12.2) years-old, a significant difference. Patients with firearms related

TSCI had significantly higher frequency of lumbar lesions and needed less often surgical treatments (See Table 2).

The ASIA and FIM scores are presented in Table 2 and Figure 2, 3, and 4. After six months, both group of patients, the group of patients with firearms related lesions and the group with other causes of TSCI showed significant improvement in ASIA SL motor scales ($F_{(1,79)}$=15.14; p<0.0001), ASIA IL motor scales ($F_{(1,79)}$=11.09; p=0.001) and FIM ($F_{(1,79)}$=84.95; p<0.0001). Patients with firearm related TSCI showed significantly better ASIA motor scores in superior limbs than patients with TSCI related to other causes ($F_{(1,79)}$=5.34; p<0.023) (Table 2 and Figure 2). However, there was no significant differences in the degree of improvement when patients with firearms related lesions where compared with the group of other causes of TSCI, a result showing that firearm TSCI lesions show similar patterns of recovery than TSCI provoked by the other causes (Table 2 and Figure 2-4). ASIA tactile scale showed only a trend to improvement ($F_{(1,79)}$=3.48; p<0.066), as well as ASIA pain scale ($F_{(1,79)}$=3.53; p<0.064), also with no significant improvement patter differences when both groups of patients where compared (Table 2 and Figure3).

Insert Table 1 about here

Insert Table 2 about here

Insert Figure 2 about here

Insert Figure 3 about here FIM

Insert Figure 4 about here FIM

Discussion

The objective of this study was report results of an evaluating functional recovery after traumatic spinal cord injury in a trauma hospital. We observed an improvement of motor skills by ASIA scale and FIM both in group who did and didn`t rehabilitation. Similar trend of FIM motor scores across different levels and completeness of injury was found in the current study when compared to other studies. (15, 16)

Traditionally, rehabilitation focuses on functional restoration by maximising residuals or returns through therapeutic exercise, or by overcoming losses with compensation techiniques and use of devices and equipment. The concept of reversing learned non-use and rediscovery of a central pattern generator (an

autonomous network of neurons capable of generating a locomotor pattern independent of supraespinal inputs) (17).

Physical rehabilitation after spinal cord injury has always been contextualized on the premise that the nervous system is irreparable and that functional improvement is associated with motor deficits compensation by the independent use of the remainder function and the use of assistive technologies such as assistive devices, wheelchairs and orthostatic boards (18-20)

The needs of everyday life, is a decisive factor for the development of spontaneous adjustments and acquisition of functional independence factor occurs even without professional supervision Ribeiro et al. (2005). In this context, the observation of functional improvement in FIM scores could be explained by the logic of optimization of the remaining functional capacity after injury, by adaptation or compensation mechanism.(20, 21)

However, new concepts about neural plasticity has expanded the prospects for recovery beyond the muscle building above the level of injury and adaptations by assistive technology. The improvement in ASIA Scale scores can not be explained by adaptations, but the plastic potential of the zones of partial preservation of each patient (19-21).

The discovery of spinal cord`s capacity for activity-dependent plasticity and afferent-based generation of locomotion after SCI in animal models led to a translation of these findings to human after SCI. Application to the human condition formed the basis for a communication across the neuroscience and clinical rehabilitation (22, 23).

For rehabilitation of patients with TSCI, the traditional emphasis on social adaptation is being expanded to include strategies that promote plasticity and

regeneration on the central nervous system. Such strategies are needed to optimize recovery of neurolgocial function (24).

Although a large number of patients might suffer from TSCI provoked by guns, this number still not known because the epidemiology of firearms related SCI have different worldwide patters and might be largely underreported. In general terms, the epidemiology of traumatic spinal cord injury is better known in the U.S., Western European countries, Australia and some parts of Asia. Cripps RA et al. mapped the TSCI epidemiology worldwide and observed that four-wheeled motor accidents were the major cause of TSCI in North America, Western Europe and Australia (25). In South-east Asia, two-wheeled (and non-standard) road transport was more common. In Southern Asia and Oceania, falls from heights were the primary causes of TSCI. On the other hand, violence, usually firearm-related TSCI is higher in North America (15%) when compared to Western Europe (6%) or Australia (2%). The highest rates of firearm-related TSCI are in Sub-Saharan (35%), North Africa (24%), Middle East (24%) and Latin America (22%). Violence-related TSCI have been frequent in zones of conflict, like Afghanistan (26). The incidence of spinal cord injury in Brazil is not well established. However, according to official governmental data, trauma is the leading cause of spinal cord pathology in Brazil (80% of all medullary lesions), with an incidence of 40/million/year (27). Vafa Rahimi-Movaghar et al. reviewed the incidence of TSCI in developing countries and found 8 studies showing an incidence of TSCI in Brazil with an incidence ranging from 10 to 71 cases per million inhabitants (28, 29). From these patients, 80% are men and 60% are between 10 and 30 years old (2). The causes of TSCI in Brazil are also not well documented, but according to recent governmental statistics (2013) the two leading causes of TSCI in Brazil are first,

vehicle accidents (with progressive lowering incidence) and second, spinal cord lesions provoked by firearms (30). Thus, unfortunately TSCI provoked by firearms is still major problem in Brazil. Programs of rehabilitation for these patients are of major importance but preventing these traumas by reducing violence is of paramount importance.

The study is a further demonstration of the considerable potential for neurologic recovery after spinal rehabilitation after TSCI. Despite the small size, our study has strengths that need to be recognized as well. It is one of the few studies designed to evaluate functional recovery after TSCI caused by gunshot. It is prospective and it is a relatively large cohort study. Moreover, patients went to a Rehabilitation Service in a hospital specialized in trauma by a team dedicated to this task. Thus, we think that in spite some limitations, our study contribute with medical literature in an area that is clearly lacking this kind of information. Thus, we hope that it might be eventfully useful regarding rehabilitation in TSCI provoked by firearms.

Conclusions:

TSCI provoked by firearms are an important cause of spinal lesion and neurological deficits in Brazil. Functional recovery in severe TSCI provoked by firearms is limited but similar than severe TSCI provoked by falls or automobilist accidents.

Conflict of interest

None declared.

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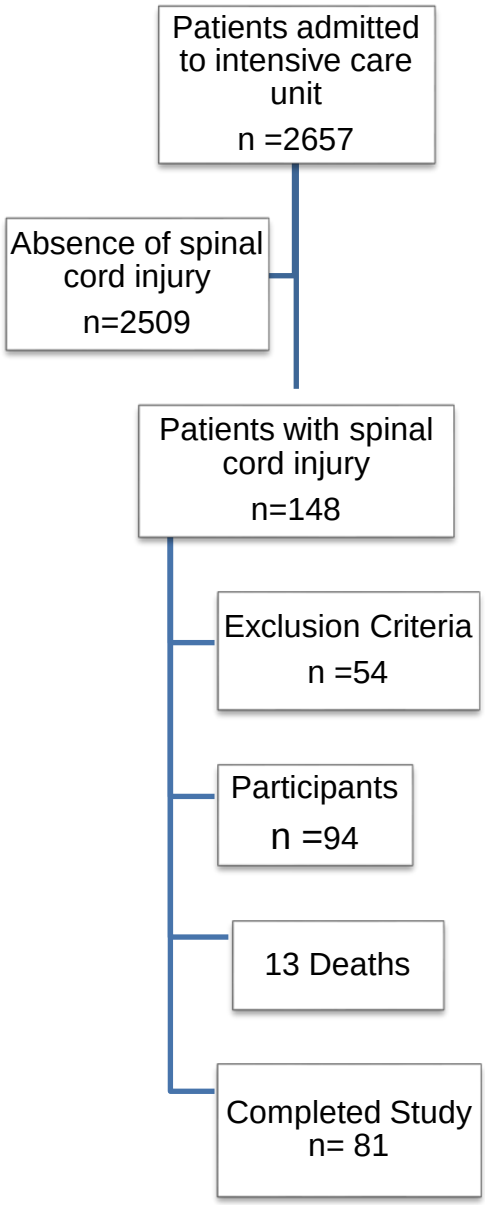

Figure 1: Flow diagram for total patients included in the study.

Table 1. Demographic and Clinical Characteristic of Patients

Variables	**All Patients**	**Cause of TSCI**			
		Weapon	**Other**	**O.R. 95% C.I.**	***p***
	***n* = 81 (100.0%)**	***n* = 31 (38.3%)**	***n* = 50 (61.7%)**		
Age (years)[a]	32.6±12.2	27.3±10.4	35.9±12.2	‘	**0.002**[b]
Days in hospital[a]	39.4±31.8	43.5±36.8	36.9±28.3	‘	0.365[b]
Days in ICU	14.3±19.2	16.9±21.4	12.7±17.6	‘	0.333 [b]
Days in MV[a]	08,0±14.1	09.4±14.7	07.1±13.7	‘	0.468[b]
Male sex – *n* (%)	76 (93.8%)	29 (93.5%)	47 (94.0%)	1.08 (0.17-6.89)	1.000[d]
Needed MV – *n* (%)	38 (46.9%)	18 (58.1%)	20 (40.0%)	2.01 (0.84-5.16)	0.113[c]
Spine Level – *n* (%)					
Cervical	39 (48.1%)	11 (35.5%)	28 (56.0%)	‘	
Thorax	32 (39.5%)	11 (35.5%)	21 (35.0%)	‘	
Lumbar	08 (09.9%)	09 (29.0%)	01 (02.0%)	‘‘	**0.001**
Surgery – *n* (%)	47 (58.0%)	07 (22.6%)	40 (80.0%)	13.7 (4.61-40.0)	**<0.0001**

TSCI = Traumatic Spinal Cord Injury; MV = Mechanical Ventilation; ICU = intensive care unit;
[a] Values are expressed as mean ± standard deviation.
[b] One way ANOVA.
[c] Pearson’s chi-square test.
Significant if $p<0.05$

Table 2. Demographic and Clinical Characteristic of Patients

	Imediate	After 6 months	Physiot.	Groups	Interaction
ASIA MOTOR SL					
Firearm	39.9 ± 15.4	43.0 ± 13.0			
Other	30.4 ± 19.6	35.4 ± 16.6	**< 0.0001**	**0.023**	0.330
ASIA MOTOR IL					
Firearm	04.0 ± 11.1	07.3 ± 13.8			
Other	05.2 ± 12.4	08.4 ± 16.0	**0.001**	0.711	0.950
ASIA TACTIL					
Firearm	58.0 ± 27.3	63.6 ± 29.3			
Other	51.3 ± 32.3	53.5 ± 28.4	0.066	0.194	0.412
ASIA PAIN					
Firearm	58.0 ± 27.3	63.6 ± 29.3			
Other	51.5 ± 32.1	53.3 ± 28.8	0.064	0.199	0.324
FIM					
Firearm	46.7±10.8	70.4±25.1			
Other	43.8±15.5	65.6±28.5	**< 0.0001**	0.373	0.697

Physioth = Physiotherapy, SL = Superior Limb, FIM = Functional Independence Measure

[a] Values are expressed as mean ± standard deviation. [b] One way ANOVA. [c] Pearson's chi-square test. Significant if $p<0.05$

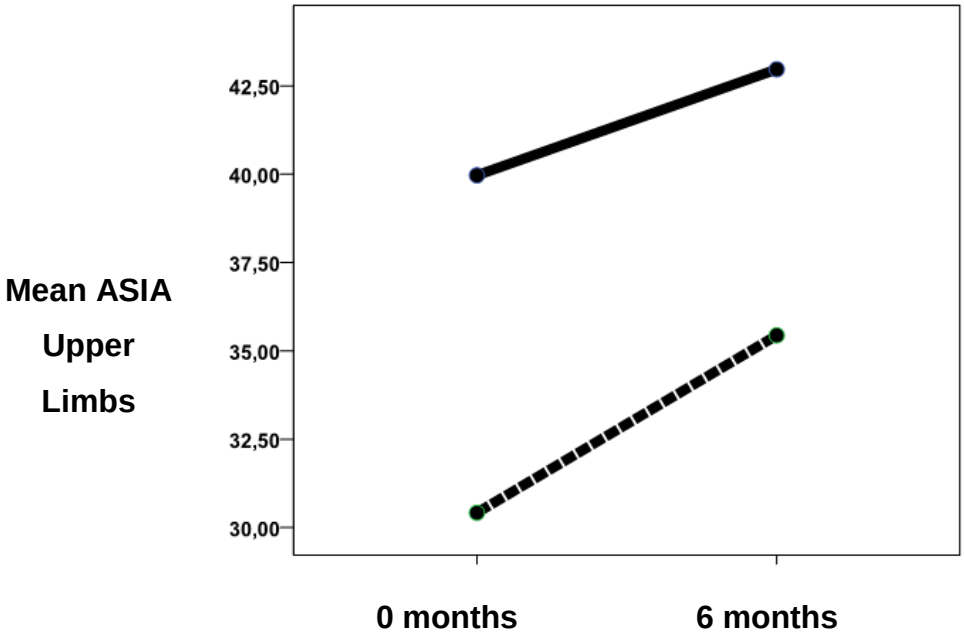

Figure 2. ASIA motor Score Upper Limbs. Comparison between TSC Weapon (dark line) and Other`s (dashed line).

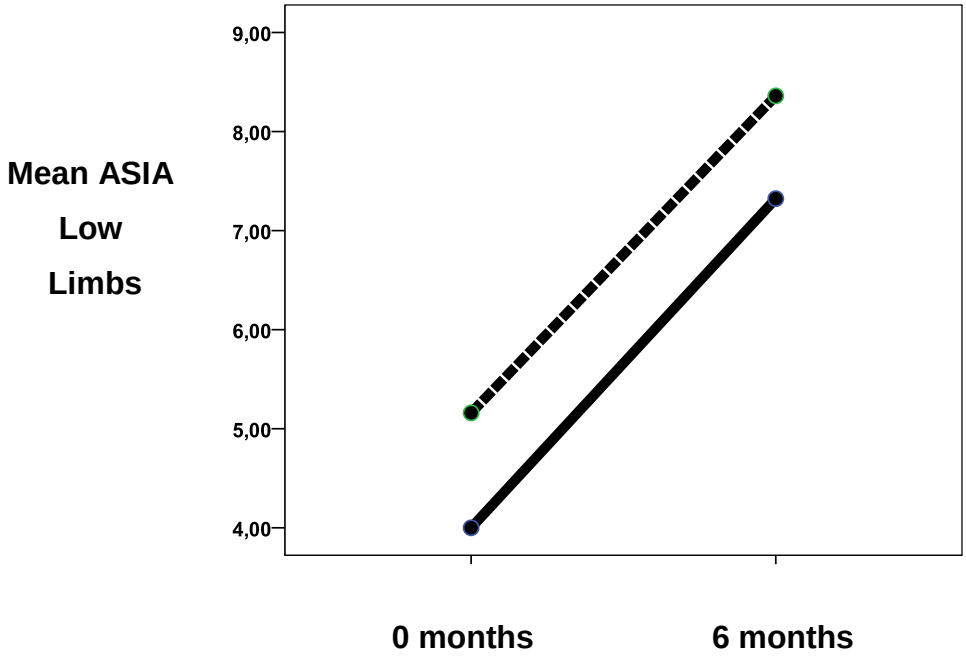

Figure 3. ASIA motor Score Low Limbs. Comparison between TSC Weapon (dark line) and Other`s (dashed line).

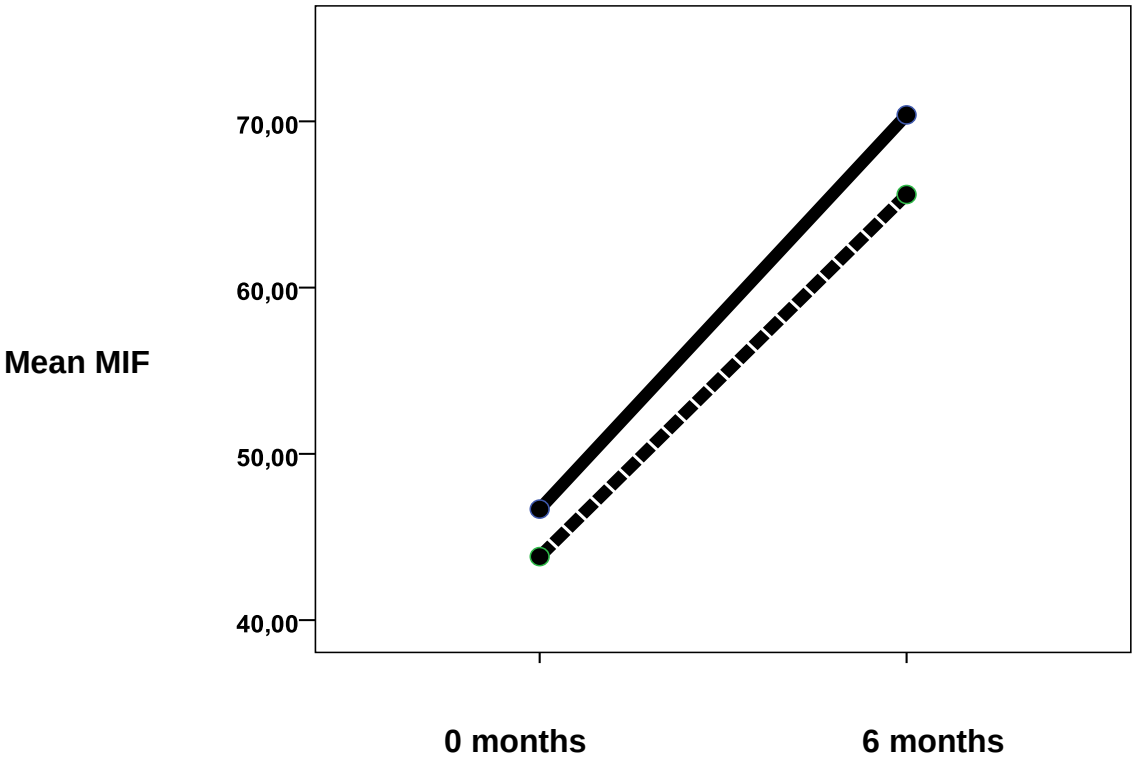

Figure 4. MIF Score. Comparison between TSC Weapon (dark line) and Other`s (dashed line).

Neuron-Specific Enolase and Interleucine-6 in Traumatic Spinal Cord Injury: A Prospective Cohort Study

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Abstract

Spinal cord injury is defined as any lesion of the spinal cord that causes neurological damage. It is a life-changing event, usually leading to permanent clinical impairment Trauma is a major and increasing cause of spinal cord injury. In spite of its importance, there are very few studies of biochemical biomarkers of traumatic spinal cord injury. This is a prospective cohort study designed to evaluate levels of NSE, IL-6 and GDNF during early traumatic spinal cord injury and its plausible impact for prognostic of these patients. Fifty-two patients were included in this study, being 90% males. Mean age was 35.08 (±14.54) years. The causes of TSCI were lesions provoked by firearm in 19 (36.5%) patients, falling in 17 (32.7%) patients, and traffic accidents in 16 (30.8%) patients. Mean of days in mechanical ventilation was 14.11 (±17.85) and mean of permanency in the intensive care unit was 20.06 (±20.23). Mortality was 19%. During first 48 after TSCI, patients showed significant increased serum levels of NSE (6.91ng/ml ± 0.87) when compared with controls (3.56ng/ml ±0.36), and IL-6 (26.34 pg.ml ± 2.92), when compared with respective controls (14.09 pg/ml ± 1.14) significant differences ($p<0.0001$ for both, NSE and IL-6) but no alterations on serum levels of GDNF. These elevations were not correlated with clinical variables or long-term prognostic of these patients. Serum levels of NSE and IL-6 are increased after different forms of TSCI and could eventually be used to evaluate new therapies that are in development.

Keywords: spinal cord injuries, biomarkers

Introduction

Spinal cord injury (SCI) is defined as any lesion of the spinal cord that causes neurological damage. It is a life-changing event, usually leading to permanent clinical impairment (Dietz, 2006) Trauma is a major and increasing cause of SCI. Epidemiological studies in the U.S. reveal an incidence of 30/40 cases per million of the population each year of traumatic spinal cord injury (TSCI) (Wyndaele et al., 2006) The incidence of SCI in developing countries is estimated to be 25.5/million/year, but it may be very variable, ranging from 2.1 to 130.7/million/year (Rahimi-Movaghar et al., 2013). The global incidence of SCI varied from 8.0 to 246.0 cases per million inhabitants per year and the global prevalence varied from 236.0 to 1,298.0 per million inhabitants (Furlan et al., 2013).

Interventions for the recovery of function following SCI include a combination of pharmacological, surgical and rehabilitation approaches. (Steeves et al., 2007, Bracken et al., 2012) Instead the diagnosis of SCI that is quite easy to make, currently there is no “cure” for paralysis in spite of intense research in this field. Differentiate the exact degree of severity and prognosticate extension of neurological recovery are challenging. For these is paramount to understand deeply the mechanism of neural damage, neuroprotection and neurological recovery.

A biomarker is a characteristic or parameter that is objectively measured and evaluated as an indicator of normal or pathologic processes or pharmacologic responses to a therapeutic intervention. Ideally, a biomarker would provide diagnostic and prognostic information. The study of biomarkers is also important for the elucidation of mechanisms of disease and for development of new therapeutic approaches. For all these reasons, biomarkers have been extensively studied in several neurological disorders, including traumatic brain injury (Woodcock et al.,

2013; Yokoboriet al., 2013). However, in spite of its importance there are very few studies of biochemical biomarkers of TSCI. Here, we report results of a prospective cohort study designed to evaluate levels of NSE, IL-6 and GDNF during early TSCI and its plausible impact for prognostic of these patients.

Methods

Patient and Controls

This was a prospective cohort study conducted in the Intensive Care Unit (ICU) of Cristo Redentor Hospital, in Porto Alegre, Brazil, from 2010 to march 2013. Porto Alegre is the capital of the state of Rio Grande does Sul in southern Brazil. The city has a population of 1,416,735 distributed in an area of 496.8 km2. Porto Alegre is the capital of Rio Grande do Sul state. It's the fourth highest Human Development Index (HDI) in the country. In Brazil, one of the largest public health systems in the world, the Unified Health System (SUS) has an agreement with almost all the hospitals . In this network are public and private university hospitals, which guarantee to all citizens the constitutional right of access to health care.

Known as the Emergency Zone North Hospital, Cristo Redentor is reference in serving accident victims, being the largest in the south of Brazil. Cristo Redentor Hospital is a 290-bed trauma care and neurosurgery regional referral center, and overall approximately 300 patients are referred to the hospital per day. The ICU functions as a closed unit, with 29 beds and care provided by physicians in routine practice and on duty, and physiotherapists during the day shift. The overall mortality rate in the hospital is 20%.

All patients (≥ 24 hours), (aged ≥ 18 years), with isolated TSCI admitted to the ICU during the period of 2010-2013 were included in this study. Exclusion criteria were head trauma or other traumas not directly associated with the spinal injury. The study was approved by the Research Ethics Committee of the institution, (#11-013), and was conducted in accordance with the provisions of the Declaration of Helsinki. Informed consent was obtained from all participants' guardians or caregivers. Our study is in accordance with the STROBE requirements.

Neurological Evaluation of Patients

Neurological Classification of Spinal Cord Injury (ASIA), through sensory and motor examination, evaluates the tactile and painful in 28 dermatomes, ranking among normal (2), decreased (1) and absence of sensory response (0). The motor examination assesses muscle strength graded from zero (no muscle contraction) to five (high force against manual resistance) in 10 specific myotomes, divided into upper and lower limbs bilaterally. The Asia scale also incorporates the Frankel scale, consisting of five levels: sensory and motor function complete (A); complete sensory and motor deficit incomplete (B), sensory and motor function incomplete nonfunctional (C); incomplete sensory and motor function functional (D) and standard motor and sensory function (E) (14)

Functional capacity was measured by means of the Functional Independence Measure (FIM), validated for the Brazilian population, which measures quantitatively the functional performance of the individual in carrying out activities that include self-care, transfers, locomotion, sphincter control and cognitive abilities. For each task is assigned a score ranging from 1 (total dependence) to 7 (complete independence).

The total score FIM ranges from 18 to 126, whereas the higher, the greater the functional capacity of the individual.

Physiotherapy Program

During the period of hospitalization the patient received 2 sessions daily physiotherapy. After discharge, the patient was referred to the Rehabilitation Service which consisted of physical, occupational and speech therapy, psychologist and also medical assistance. Outpatient program included a minimum of 6 weeks, 3 times a week.

The Physiotherapy Activities during the hospital were: airway and respiratory management (non-invasive ventilation, deep breathing exercises, bronchial hygiene) musculoskeletal treatment modalities (body positioning, range of motion/stretching exercises, endurance exercises), skin management, mobility training (bed mobility, wheelchair mobility, gait, transfers), strengthening exercises, upright work. After discharge the patient was referred to the Rehabilitation Service which was added equipment evaluation and educations as well as they were invited to participated in interdisciplinary conferences.

Samples and Biochemical Dosages

Blood samples (5 ml) from patients and controls were collected without anticoagulant and sera were frozen at -70°C until analyzed. The BiotrakTM human (h) IL-6 ELISA system from Amersham Biosciences was used for measuring IL-6 in serum of all patients and controls. The optical density was determined at 450 nm. Serum NSE was measured using an eletrochemilumines- cent assay provided by Roche DiagnosticsR, Indianapolis, IN, a double sandwich assay that uses an

antibody anti- NSE bound with ruthenium (luminescent label). The reaction and quantification were performed by Elecsys- 2010 (Roche). No hemolyzed samples were used.

All assay were carried out in duplicates and the confidence variance was within 5%.

Statistical analysis

Continuous variables were analyzed by the Student t-test with Levene's test to assess the equality of variances or Mann-Whitney test, depending on the normality of data distribution and results are expressed in mean (±SD). Correlations between serum biomarkers and other variables were done with Person and y test, depending on the normality of data. Categorical variables were analyzed by the Chi-square test. All statistical analyses were performed using the SPSS version 20 software (IBM Corp., 2011, USA). In all analysis a significant difference was considered at $p<0.05$.

Results

Fifty-two patients were included in this study, being 90% males. Mean age was 35.08 (±14.54) years. The causes of TSCI were lesions provoked by firearm in 19 (36.5%) patients, falling in 17 (32.7%) patients, and traffic accidents in 16 (30.8%) patients. Mean of days in mechanical ventilation was 14.11 (±17.85) and mean of permanency in the intensive care unit was 20.06 (±20.23). Mortality was 19%. (Table 1). Patients with lesions provoked by gunshots presented more often thorax lesions and less commonly needed surgical intervention. After falls, cervical lesions predominate and patients showed greater neurological impairment (Table 2). During first 48 after TSCI, patients showed significant increased serum levels of NSE (6.91ng/ml ± 0.87) when

compared with controls (3.56ng/ml ±0.36), (Figure 1A) and IL-6 (26.34 pg.ml ± 2.92), when compared with respective controls (14.09 pg/ml ± 1.14) (Figure 1B), a significant difference (both $p<0.0001$) but no alterations on serum levels of GDNF (Figure 1C). However, these elevations were not correlated with clinical variables or long-term prognostic of these patients (Table 3).

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Discussion

In our study, patients with TSCI showed increased levels of NSE and IL-6 during the first 48 hours after trauma. Levels of GDNF were not different from controls. The increase of NSE and IL-6 did not correlate with clinical parameters studied or clinical outcome of patients.

Biochemical biomarkers of SCI are not frequently reported in literature, in spite of its potential importance for understanding physiopathology of SCI, prognostic, or for development of new treatments. In a recent review that included all studies humans and animal models, published and listed in MEDLINE from 1991 to 2013, Yokobori et al. were able to find only 12 articles that included the descriptions of protein and structural biomarkers for the evaluations of spinal cord injury (Yokobori et al. 2013). Additionally, other few studies have been reported other biochemical parameters, mainly inflammation-related biomarkers (Woodcock et al., 2013). So far, the most studied biochemical biomarkers in SCI are S100-beta, NSE, and glial fibrillary acidic protein (GFAP) (van Dongen et al., 1998; van Dongen EP et al., 1999; Brisby et al., 1999; Marquardt et al., 2004a; Marquardt et al., 2004b; Brunnekreef et al., 2007; Winnerkvist et al., 2007; Lee et al., 2010; Khaladj et al., 2008; Marquardt et al., 2009; Pouw et al., 2009). Other biomarkers that have been studied in TSCI include neurofilaments, myelin basic protein, ubiquitin C-terminal hydrolase-L1 and a-II spectrin breakdown products, tau protein, MCP-1, and pro-inflammatory or anti-inflammatory cytokines (Ohta et al., 2002; Guez et al., 2003; Shiiya et al., 2004; Kwon et al., 2010; Yu et al., 2011; Yokobori et al., 2013). These studies showed variable serum or CSF changes, but few of them have studied prognostic significance of these variations.

In humans, first studies of biochemical markers of spinal cord injury evaluated levels of S100-beta in serum or CSF during thoracoabdominal aortic aneurysm surgery with the objective of study of biochemical marker of spinal cord ischemia (van Dongen et al., 1998; van Dongen et al., 1999). Since than, others authors have reported increase of S100-beta, NSE or GFAP in spinal cord pathologies like lumbar disk herniation (Brisby et al., 1999), paresis due to spinal metastasis (Marquardt et al., 2004a) or spinal epidural empyema (Marquardt et al., 2004b). Although levels of these biomarkers have been elevated, and some findings suggest that these could be related with long-term outcome, these earlier studies were inconclusive about prognostic use of biomarker in TSCI.

As far as we could track, only four previous studies evaluated CSF or serum biomarkers of TSCI. Guez et al. were among the first to reported CSF biomarkers in human TSCI (Guez et al., 2003). In this seminal study, CSF concentrations of NFL (neurofilament light chain) and GFAP (glial fibrillary acid protein) were significantly increased in patients when compared with controls and patients with more sever lesions seemed to show higher levels of NFL and GFAP, although no statistical analysis was performed. Latter, Know et al. in a prospective and well-designed study described temporal pattern of expression of several inflammatory cytokines in cerebrospinal fluid after acute TSCI and evaluated its potential use as parameter of injury severity or its use as prognostic factors (Kwon et al., 2010). These authors obtained CSF and blood samples over a period of 72 hours in 27 TSCI patients with complete lesions (ASIA A) or incomplete lesions (ASIA B or C). Cytokines and proteins were measured and compared among three injury severities (ASIA A, B, and C). The CSF concentrations of three putative biomarkers (S100b, GFAP, IL-8) were able to classify the injury severity of the patients, and predicted motor outcome after

6 months better than the clinical evaluation. Similar to our observations, these authors observed CSF increase of IL-6 but could not correlate this increase with clinical outcome. Hayakawa et al. evaluated plasma concentrations of a biomarker for axonal injury, phosphorylated form of the high-molecular-weight neurofilament subunit NF-H (pNF-H) in 14 patients with acute cervical SCI . These authors observed elevated plasma pNF-H according with the severity of SCI, suggesting that pNF-H levels could reflect the magnitude of axonal damage (Hayakawa et al., 2012). In this study, the levels of pNF-H were statistically different in patients with complete SCI and incomplete SCI, suggesting a diagnostic and a prognostic value for pNF-H in TSCI. More recently, Yokobori et al. measured ubiquitin C-terminal hydrolase-L1 and a-II spectrin breakdown and GFAP in CSF or serum of seven TSCI patients and 15 controls (Yokobori et al., 2013). These authors report increased levels of these compounds in TSCI patients and observed some correlation between CSF or serum levels of GFAP and severity of lesion and degree of recovery of patients.

NSE is a 78-kDa dimeric g-isoenzyme of the glycolytic enzyme enolase, mainly located in neuron cytoplasm. In physiological conditions it is usually not secreted to extracellular fluids, but it has been reported to increase in CSF or serum in patients with neurological pathologies, including trauma (Cooper et al., 1994; Butterfield et al., 2009; Gerlt et al., 2012). Pre-clinical and clinical studies have been showing that NSE increases in serum or CSF after TBI or TSCI, in a time dependent manner, according with severity of the injury suggesting possible prognostic value for NSE in trauma (Yokobori, et al., 2013a; Yokoboriet al., 2013b) NSE has been show to be increased in human TBI and some studies suggest that elevation of NSE in TBI might have also prognostic significance. So far, few authors have studied NSE in human spine pathologies. Brisby et al. measured CSF concentration of NSE in

lumbar disc surgery, and observed that patients with lumbar disc herniation had significantly high concentrations of NSE. We were not able to find previous evaluations of NSE in TSCI (Brisby et al., 1999). In our study NSE was elevated in serum of patients with TSCI but we were unable to observe a correlation between this elevation with clinical variables or prognostic aspects.

Interlekine-6 is a B-cell differentiation factor that has neurotrophin-like effects having a role in normal CNS physiological processes as well as in several neurological disorders (Erta et al., 2012). In CNS, IL-6 is upregulated with neuroinflammation, as observed after CNS infection or injury in a number of CNS diseases (Erta et al., 2012). In humans, IL-6 increases in both, CSF and serum after TBI, but its prognostic value remains unknown (Woodcock et al., 2013) While some authors have correlated higher levels of IL-6 with poor prognosis in TBI, other have failed in finding such association or reported that increased of IL-6 favor better outcomes (Woodcock et al., 2013). As far as we know, there is only one previous report of IL-6 in human TSCI (Kwon et al., 2010). In this study, the levels of CSF IL-6 could not be correlated with clinical outcome. Here we observed a similar situation. In spite of a robust increase of IL-6 in serum, it did not correlated with clinical variables or long-term-outcome.

Our study has limitations and we recognize it. We evaluated only three different biomarkers and only during the acute period of TSCI. However it has some strength that need to be recognized as well. It is a cohort prospective study that included a relatively large number of patients that were followed for at least six months. Also, we evaluated patients with gunfire spinal chord lesion, a group hardly included in TSCI biomarkers studies. In our study, we observe a robust increase of NSE and IL-6, but not GDNF, in serum of these patients and this increase was not

related with severity of the trauma or its prognosis. Even that, we conclude that serum levels of NSE and IL-6 are increased after different forms of TSCI and could eventually be used to evaluate new therapies that are in development.

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Table 1. Characteristics of Patients

Variables	Total n = 52
Age (years)[a]	35.08 ±14.54
Days in ICU[a]	20.06±20.23
Days in MV	14.11±17.85
Male sex – n (%)	47 (90.4%)
Survivals	42 (80.8%)
Cause	
Firearm	19 (36.5%)
Fall	17 (32.7%)
Motorcycle Accident	16 (30.8%)
Spine Level	
Cervical	26 (50.0 %)
Thorax	26 (50.0%)

[a] Values are expressed as mean ± standard deviation.

MV = mechanical ventilation

Table 2. Clinical Variables According with Cause of Spinal Cord Injury

Variables	Cause of TSCI			*p*
	Weapon	**Fall**	**Car**	
	n=19 (%)	**n=17 (%)**	**n=16 (%)**	
Age (years)[a]	32.10±13.39	36.47±17.11	37.12±13.19	0.540[b]
Days in hospital[a]	49.79±38.08	33.76±27.33	45.93±34.02	0.347[b]
Days in ICU	21.84±18.81	21.23±19.42	16.69±23.40	0.731
Days in MV[a]	15.53±17.79	15.59±17.85	10.87±17.64	0.692[b]
Male sex – n (%)	17 (89.5%)	16 (94.1%)	14 (87.5%)	0.801[c]
Survivals	16 (84.2%)	11 (64.7%)	15 (93.8%)	0.095[c]
Spine Level				
Cervical	05 (26.3%)	14 (82.4%)	07(43.8%)	
Thorax	14 (73.7%)	03 (17.6%)	09 (56.3%)	**0.003***
Surgery	04 (21.1%)	11 (64.7%)	13 (81.3%)	**0.001***
Frankel A	14 (73.7%)	11 (64.7%)	08 (50.0%)	0.347[c]
Asia Motor Upper Limb	40.79±16.28	16.47±18.63	36.56±19.08	**<0.0001***
Asia Motor Lower Limb	03.89±12.08	05.18±12.73	09.19±16.36	0.509[b]
Asia Tactile	53.00±22.94	40.77±37.23	60.81±31.16	0.177[b]
Asia Pain	53.00±22.94	40.76±37.23	60.56±31.34	**0.184**

TSCI = Traumatic Spinal Cord Injury; MV = Mechanical Ventilation;

[a] Values are expressed as mean ± standard deviation. (*) significant.

Table 3. Clinical Variabels of TSCI Patients and Biomarkers

	NSE		GDNF		IL-6	
	Mean SD	***p***	**Mean SD**	***p***	**Mean SD**	***p***
Cause						
Accident	5.05 (3.07)		14.30 (13.42)		37.64 (12.97)	
Fall	5.62 (4.51)		15.63 (18.41)		35.01 (18.99)	
Fire Arm	9.62 (8.55)	0.056	16.54 (11.88)	0.910	16.55 (09.28)	0.335
Level Lesion						
Cervical	6.78 (4.56)		13.49 (11.66)		26.15 (17.35)	
Thoraxic	7.04 (7.71)	0.879	17.53 (17.31)	0.333	37.16 (46.92)	0.347
Frankel						
Frankel A	6.77 (6.53)		16.62 (17.03)		35.74 (41.59)	
Other	7.15 (5.97)	0.839	13.49 (09.67)	0.470	23.57 (14.60)	0.317
Evolution						
Survived	6.98 (6.40)		16.06 (15.08)		30.12 (37.55)	
Died	6.60 (6.01)	0.865	12.89 (13.12)	0.896	35.66 (22.25)	0.695
Correlations	**CC**	***p***	**CC**	***p***	**CC**	***p***
Age	-0.100	0.481	0.041	0.775	0.114	0.508
Days in Hospital	-0.066	0.643	0.186	0.200	-0.059	0.773
Days in UCI	-0.041	0.775	0.131	0.365	0.295	0.081
Days in MV	-0.079	0.579	0.240	0.094	0.022	0.091
Asia Motor Upper Limb	0.091	0.522	0.217	0.131	0.158	0.359
Asia Motor Lower Limb	0.099	0.484	0.060	0.681	-0.137	0.425
Asia Tactile	0.096	0.499	-0.068	0.640	-0.080	0.641
Asia Pain	0.096	0.500	-0.067	0.645	-0.790	0.653
Mif1	-0.056	0.696	-0.058	0.692	0.012	0.942

CC= Correlation coefficient. (*) significant.

Figure 1A – NSE

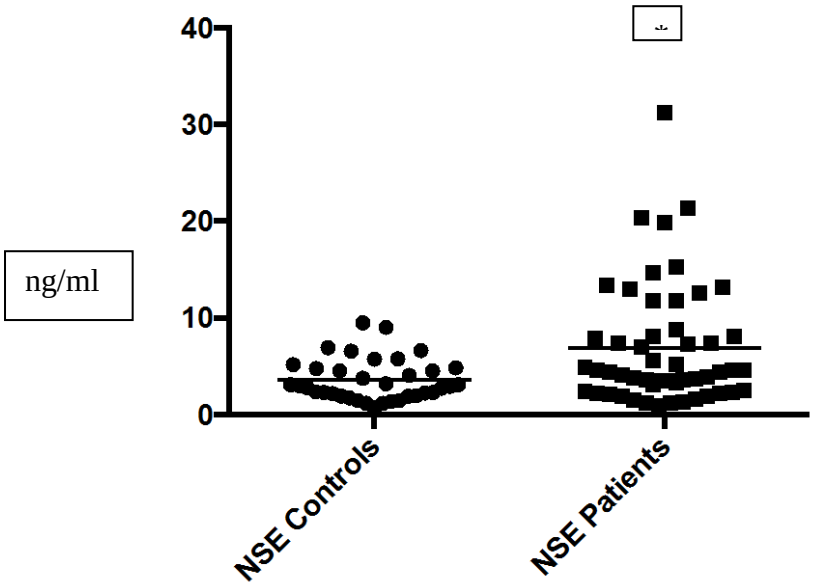

Figure 1A. First 48 hours serological expression of Neuron Specific Enolase (NSE) after human spinal cord injury (SCI). Comparison between NSE Control and Patients. * p <0,05

Figure 1 B - IL-6

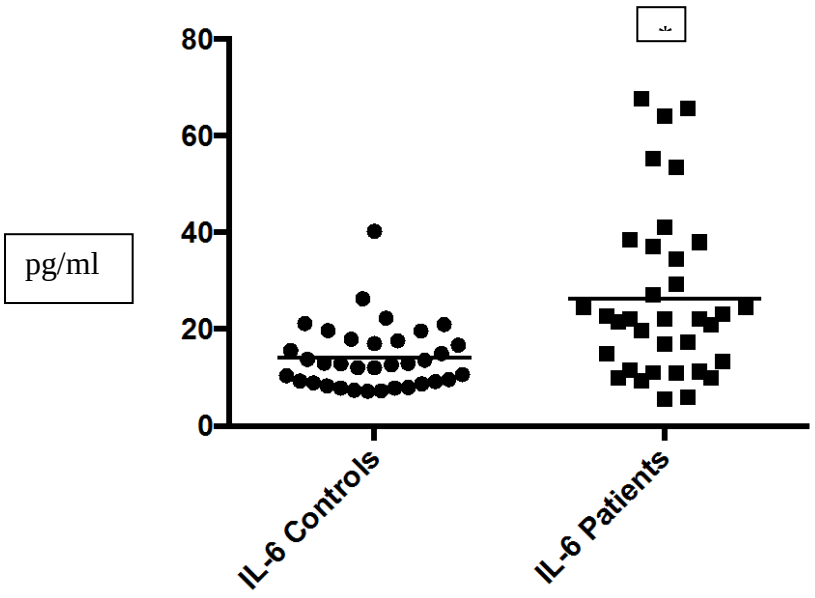

Figure 1 B First 48 hours serological expression Interleucin-6 (IL-6) after human spinal cord injury (SCI). Comparison between IL-6 Control and Patients. * p <0,05

Figure 1C – GDNF

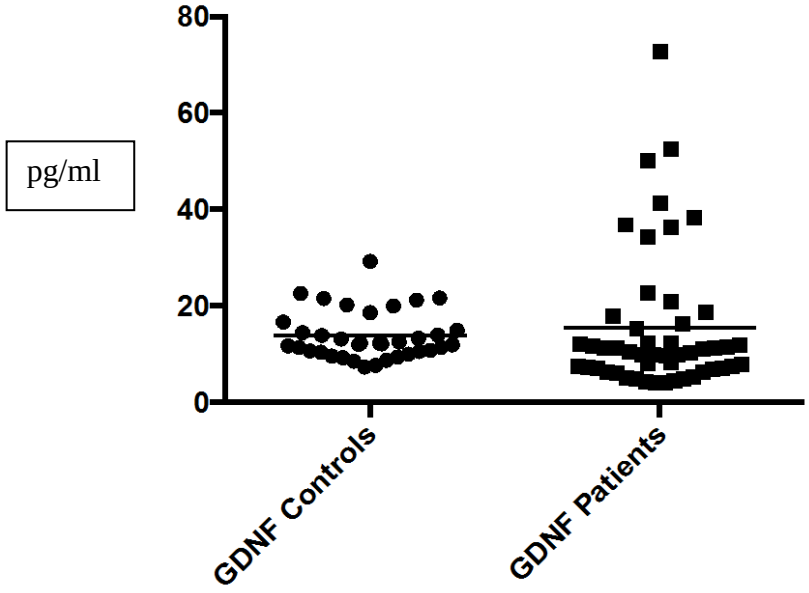

Figure 1 C First 48 hours serological expression GDNF after human spinal cord injury (SCI). Comparison between Control and Patients. $p<0.851$

6 – Considerações Finais

A incidência de lesões medulares por arma de fogo é alta em nosso meio. Neste trabalho foi possível avaliar a incidência destas lesões em um hospital referência em trauma e reabilitação.

Observaram-se melhoras no desempenho motor e funcional destes pacientes a partir de um acompanhamento desde a Unidade de Terapia Intensiva até seis meses após a alta hospitalar, incluindo o processo de Reabilitação. A melhora funcional dos pacientes com lesão por arma de fogo foi similar à de pacientes com lesões medulares por outras causas.

A avaliação do comportamento dos biomarcadores permite uma abordagem rápida quando realizada por meio de coleta sanguínea e pode estabelecer uma relação direta com a gravidade da lesão. Isso nos nao encontramos

Considerando a avaliação limitada do prognóstico sensitivo em pacientes com lesão medular, é nossa opinião que novos estudos clínicos devem ser realizados avaliando a aplicabilidade de biomarcadores como ferramenta de diagnóstico e prognóstico.